



Results

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About 105 Papers from more than 30 Journals are cited.

1	APPLICATIONS (69)	Page 2	
1.1	Small Molecules (7)		
	Med. Chem. And Drug Design	Page 2	
1.2	Biopolymers (62)		
	Bioinformatics and Cheminformatics	Page 4	Enzyme Catalysis Page 12
	Comparitive or Homology Modeling	Page 6	Protein-Protein Interactions Page 15
	Protein Conformational Analysis	Page 7	Membrane Proteins Page 16
	Protein Structure Analysis	Page 9	Protein Folding Page 19
	Protein Dynamics	Page 9	Protein-Nucleic Acids Page 20
	Ligand Binding	Page 11	Nucleic Acids Page 21
1.3	Polymers		
1.4	Surfaces, Catalysts and Material	Page 21	
2	METHODOLOGY (25)	Page 22	
	QSAR	Page 22	QM & QM/MM Page 25
	Potentials and Parameters	Page 23	Comparative or Homology Page 27
	Molecular Dynamics	Page 24	Ligand Docking Page 27
	Monte Carlo	Page 25	
3	JOURNAL REVIEWS (3)	Page 30	
	Journal of Computational Chemistry, 36 (1), January, 2015.		
	Journal of Computational Chemistry, 36 (2), January, 2015.		
	Journal of Molecular Modeling, 20 (12), December, 2014.		
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 38	
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION		

1. APPLICATIONS

1.1. Small Molecules

Medicinal Chemistry and Drug Design

Chroman-4-one- and Chromone-Based Sirtuin 2 Inhibitors with Antiproliferative Properties in Cancer Cells

Tina Seifert, Marcus Malo, Tarja Kokkola, Karin Engen, Maria Fridén-Saxin, Erik A. A. Wallén, Maija Lahtela-Kakkonen, Elina M. Jarho, Kristina Luthman [University of Gothenburg]

J.Med.Chem., 57, 9870–9888, 2014.

Sirtuins (SIRT2s) catalyze the NAD⁺-dependent deacetylation of Nε-acetyl lysines on various protein substrates. SIRT2s are interesting drug targets as they are considered to be related to important pathologies such as inflammation and aging-associated diseases. We have previously shown that chroman-4-ones act as potent and selective inhibitors of SIRT2. Herein we report novel chroman-4-one and chromone-based SIRT2 inhibitors containing various heterofunctionalities to improve pharmacokinetic properties. The compounds retained both high SIRT2 selectivity and potent inhibitory activity.

Creating and virtually screening databases of fluorescently-labelled compounds for the discovery of target-specific molecular probes

Rhiannon L. Kamstra, Saedeh Dadgar, John Wigg, Morshed A. Chowdhury, Christopher P. Phenix, Wely B. Floriano [Lakehead University]

J.Comp.Aided. Mol.des. 28, 1129-1142, 2014.

Our group has recently demonstrated that virtual screening is a useful technique for the identification of target-specific molecular probes. In this paper, we discuss some of our proof-of-concept results involving two biologically relevant target proteins, and report the development of a computational script to generate large databases of fluorescence-labelled compounds for computer-assisted molecular design. The virtual screening of a small library of 1,153 fluorescently-labelled compounds against two targets, and the experimental testing of selected hits reveal that this approach is efficient at identifying molecular probes, and that the screening of a labelled library is preferred over the screening of base compounds followed by conjugation of confirmed hits.



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Medicinal Chemistry and Drug Design (Cont'd)

Identification of novel peroxisome proliferator-activated receptor-gamma (PPAR γ) agonists using molecular modeling method

Veronica M. W. Gee, Fiona S. L. Wong, Lalitha Ramachandran, Gautam Sethi, Alan Prem Kumar [National University of Singapore], Chun Wei Yap

J.Comp.Aided. Mol.des. **28**, 1143-1151, 2014.

Peroxisome proliferator-activated receptor-gamma (PPAR γ) plays a critical role in lipid and glucose homeostasis. It is the target of many drug discovery studies, because of its role in various disease states including diabetes and cancer. Thiazolidinediones, a synthetic class of agents that work by activation of PPAR γ , have been used extensively as insulin-sensitizers for the management of type 2 diabetes. In this study, a combination of QSAR and docking methods were utilised to perform virtual screening of more than 25 million compounds in the ZINC library.

Structure-Activity Relationships of a Novel Capsid Targeted Inhibitor of HIV-1 Replication

Sandhya Kortagere, Jimmy P. Xu, Marie K. Mankowski, Roger G. Ptak, Simon Cocklin[Drexel University College of Medicine]

J.Chem. Infor. and Mod. **54**, 3080–3090, 2014.

Despite the considerable successes of highly active antiretroviral therapy (HAART) for the treatment of HIV/AIDS, cumulative drug toxicities and the development of multidrug-resistant virus necessitate the search for new classes of antiretroviral agents with novel modes of action. The HIV-1 capsid (CA) protein has been structurally and functionally characterized as a druggable target. We have recently designed a novel small molecule inhibitor I-XW-053 using the hybrid structure based method to block the interface between CA N-terminal domains (NTD–NTD interface) with micromolar affinity.

Improving the Use of Ranking in Virtual Screening against HIV-1 Integrase with Triangular Numbers and Including Ligand Profiling with Antitargets

Alfonso T. García-Sosa[University of Tartu] , Uko Maran

J.Chem. Infor. and Mod. **54**, 3172–3185, 2014.

A delicate balance exists between a drug molecule's toxicity and its activity. Indeed, efficacy, toxicity, and side effect problems are a common cause for the termination of drug candidate compounds and development projects. To address this, an antitarget interaction profile is built and combined with virtual screening and cross docking for new inhibitors of HIV-1 integrase, in order to consider possible off-target interactions as early as possible in a drug or hit discovery program. New ranking techniques using triangular numbers improve ranking information on the compounds and recovery of known inhibitors into the top compounds using different docking programs.

Discovering New Agents Active against Methicillin-Resistant Staphylococcus aureus with Ligand-Based Approaches

Ling Wang, Xiu Le, Long Li, Yingchen Ju, Zhongxiang Lin, Qiong Gu, and Jun Xu [Sun Yat-Sen University]

J.Chem. Infor. and Mod. **54**, 3186–3197, 2014.

To discover new agents active against methicillin-resistant Staphylococcus aureus (MRSA), in silico models derived from 5451 cell-based anti-MRSA assay data were developed using four machine learning methods, including naïve Bayesian, support vector machine (SVM), recursive partitioning (RP), and k-nearest neighbors (kNN). A total of 876 models have been constructed based on physicochemical descriptors and fingerprints. The overall predictive accuracies of the best models exceeded 80% for both training and test sets.

Medicinal Chemistry and Drug Design (Cont'd)

A data-driven approach to modeling the tripartite structure of multidrug resistance efflux pumps

Joshua L. Phillips , S. Gnanakaran[Los Alamos National Labs]

Proteins: Stru. Fun. & Bioinf., **83**, 46–65, 2015.

Many bacterial pathogens are becoming increasingly resistant to antibiotic treatments, and a detailed understanding of the molecular basis of antibiotic resistance is critical for the development of next-generation approaches for combating bacterial infections. An atomic-level resolution tripartite structure remains imperative to advancing our understanding of the molecular mechanisms of pump function using both theoretical and experimental approaches. We develop a fast and consistent method for constructing tripartite structures which leverages existing data-driven models and provide molecular modeling approaches for constructing tripartite structures of multidrug resistance efflux pumps.

1.2. Biopolymers

Bioinformatics and Cheminformatics

SCDFinder, a Web-based tool for the identification of putative novel ATM and ATR targets

Lukas Cara, Medina Baitemirova, Franklin Duong, Maia Larios-Sanz[University of St. Thomas], Albert Ribes-Zamora

Bioinformatics. **30**, 3394-3395, 2014.

The S/TQ cluster domain (SCD) constitutes a new type of protein domain that is not defined by sequence similarity but by the presence of multiple S/TQ motifs within a variable stretch of amino acids. SCDs are recognized targets for DNA damage response (DDR) kinases like ATM and ATR. Characterizing DDR targets is of significant interest. The aim of this work was to develop a web-based tool to allow for easy identification and visualization of SCDs within specific proteins or in whole proteome sets, a feature not supported by current domain and motif search tools.

Poretools: a toolkit for analyzing nanopore sequence data

Nicholas J. Loman , Aaron R. Quinlan[University of Virginia]

Bioinformatics. **30**, 3399-3401, 2014.

Nanopore sequencing may be the next disruptive technology in genomics, owing to its ability to detect single DNA molecules without prior amplification, lack of reliance on expensive optical components, and the ability to sequence long fragments. The MinION™ from Oxford Nanopore Technologies (ONT) is the first nanopore sequencer to be commercialized and is now available to early-access users. The MinION™ is a USB-connected, portable nanopore sequencer that permits real-time analysis of streaming event data. Currently, the research community lacks a standardized toolkit for the analysis of nanopore datasets.

Bioinformatics and Cheminformatics (Cont'd)

PyBamView: a browser-based application for viewing short read alignments

Melissa Gymrek[Broad Institute of MIT and Harvard]

Bioinformatics. **30**, 3405-3407, 2014.

Current sequence alignment browsers allow visualization of large and complex next-generation sequencing datasets. However, most of these tools provide inadequate display of insertions and can be cumbersome to use on large datasets. I implemented PyBamView, a lightweight Web application for visualizing short read alignments. It provides an easy-to-use Web interface for viewing alignments across multiple samples, with a focus on accurate visualization of insertions.

Visually impaired researchers get their hands on quantum chemistry: application to a computational study on the isomerization of a sterol

Valère Lounnas, Henry B. Wedler [University of California – Davis], Timothy Newman, Gijs Schaftenaar, Jason G. Harrison, Gabriella Nepomuceno, Ryan Pemberton, Dean J. Tantillo, Gert Vriend

J.Comp.Aided. Mol.des. **28**, 1057-1067, 2014.

In molecular sciences, articles tend to revolve around 2D representations of 3D molecules, and sighted scientists often [RESORT](#) to 3D virtual reality software to study these molecules in detail. Blind and visually impaired (BVI) molecular scientists have access to a series of audio devices that can help them read the text in articles and work with computers. Reading articles published in this journal, though, is nearly impossible for them because they need to generate mental 3D images of molecules, but the article-reading software cannot do that for them. We have previously designed AsteriX, a web server that fully automatically decomposes articles, detects 2D plots of low molecular weight molecules, removes meta data and annotations from these plots, and converts them into 3D atomic coordinates.

DMG- α —A Computational Geometry Library for Multimolecular Systems

Robert Szczelina[Jagiellonian University], Krzysztof Murzyn

J.Chem. Infor. and Mod. **54**, 3112–3123, 2014.

The DMG- α library grants researchers in the field of computational biology, chemistry, and biophysics access to an open-sourced, easy to use, and intuitive software for performing fine-grained geometric analysis of molecular systems. The library is capable of computing power diagrams (weighted Voronoi diagrams) in three dimensions with 3D periodic boundary conditions, computing approximate projective 2D Voronoi diagrams on arbitrarily defined surfaces, performing shape properties recognition using α -shape theory and can do exact Solvent Accessible Surface Area (SASA) computation.

Molecular damage in Fabry disease: Characterization and prediction of alpha-galactosidase A pathological mutations

Casandra Riera, Sergio Lois, Carmen Domínguez, Israel Fernandez-Cadenas, Joan Montaner, Victor Rodríguez-Sureda, Xavier de la Cruz[Vall d'Hebron Institute of Research (VHIR)]

Proteins: Stru. Fun. & Bioinf., **83**, 91–104, 2015.

Loss-of-function mutations of the enzyme alpha-galactosidase A (GLA) causes Fabry disease (FD), that is a rare and potentially fatal disease. Identification of these pathological mutations by sequencing is important because it allows an early treatment of the disease. However, before taking any treatment decision, if the mutation identified is unknown, we first need to establish if it is pathological or not. General bioinformatic tools (PolyPhen-2, SIFT, Condel, etc.) can be used for this purpose, but their performance is still limited. Here we present a new tool, specifically derived for the assessment of GLA mutations.

Comparative or Homology Modeling

Reversible Ketomethylene-Based Inhibitors of Human Neutrophil Proteinase 3

Adnan Budnjo, Shailesh Narawane, Cédric Grauffel, Anne-Sophie Schillinger, Torgils Fossen, Nathalie Reuter[University of Bergen], Bengt Erik Haug

J.Med.Chem., **57**, 9396–9408, 2014.

Neutrophil serine proteases, proteinase 3 (PR3) and HUMAN neutrophil elastase (HNE), are considered as targets for chronic inflammatory diseases. Despite sharing high sequence similarity, the two enzymes have different substrate specificities and functions. While a plethora of HNE inhibitors exist, PR3 specific inhibitors are still in their infancy. We have designed ketomethylene-based inhibitors for PR3 that show low micromolar IC₅₀ values. Their synthesis was made possible by amending a previously reported synthesis of ketomethylene dipeptide isosteres to allow for the preparation of derivatives suitable for solid phase peptide synthesis.

Serendipitous Discovery of Short Peptides from Natural Products as Tyrosinase Inhibitors

Nai-Wan Hsiao, Tien-Sheng Tseng, Yu-Ching Lee, Wang-Chuan Chen, Hui-Hsiung Lin, Yun-Ru Chen, Yeng-Tseng Wang, Hung-Ju Hsu, Keng-Chang Tsai [National Changhua University of Education]

J.Chem. Infor. and Mod. **54**, 3099–3111, 2014.

Tyrosinase, which is the crucial copper-containing enzyme involved in melanin synthesis, is strongly associated with hyperpigmentation disorders, cancer, and neurodegenerative disease; thus, it has attracted considerable interest in the fields of medicine and cosmetics. The known tyrosinase inhibitors show numerous adverse side effects, and there is a lack of safety regulations governing their use. As a result, there is a need to develop novel inhibitors with no toxicity and long-term stability. In this study, we use molecular docking and pharmacophore modeling to construct a reasonable and reliable pharmacophore model, called Hypo 1, that could be used for identifying potent natural products with crucial complementary functional groups for mushroom tyrosinase inhibition.

Structure and Ligand-Based Design of mTOR and PI3-Kinase Inhibitors Leading to the Clinical Candidates VS-5584 (SB2343) and SB2602

Anders Poulsen [Experimental Therapeutics Centre, Agency for Science, Technology and Research, 31 Biopolis Way], Harish Nagaraj, Angeline Lee, Stéphanie Blanchard, Chang Kai Soh, Dizhong Chen, Haishan Wang, Stefan Hart, Kee Chuan Goh, Brian Dymock, and Meredith Williams

J.Chem. Infor. and Mod. **54**, 3238–3250, 2014.

Phosphoinositide 3-kinases (PI3Ks) and the mammalian target of rapamycin (mTOR) act as critical effectors in a commonly deregulated cell signaling pathway in human cancers. The abnormal activation of the PI3K/mTOR pathway has been shown to play a role in initiation, progression, and metastasis of human tumors. Being one of the most frequently activated pathways in cancer, much effort has been directed toward inhibition of the PI3K/mTOR pathway as a novel oncology therapy. Previous work by a number of groups has revealed several selective PI3K and dual mTOR/PI3K inhibitors. However, there are few reports of therapeutic agents with a pan-PI3K/mTOR inhibitory profile within a narrow concentration range.

Comparative or Homology Modeling (Cont'd)

γ S-Crystallin Proteins from the Antarctic *Nototheniid* Toothfish: A Model System for Investigating Differential Resistance to Chemical and Thermal Denaturation

Carolyn N. Kingsley, Jan C. Bierma, Vyvy Pham, Rachel W. Martin [University of California—Irvine]

J. Phys. Chem. B., **118**, 13544–13553, 2014.

The γ S1- and γ S2-crystallins, structural eye lens proteins from the Antarctic toothfish (*Dissostichus mawsoni*), are homologues of the human lens protein γ S-crystallin. Although γ S1 has the higher thermal stability of the two, it is more susceptible to chemical denaturation by urea. The lower thermodynamic stability of both toothfish crystallins relative to human γ S-crystallin is consistent with the current picture of how proteins from organisms endemic to perennially cold environments have achieved low-temperature functionality via greater structural flexibility.

Protein Conformational Analysis

The Theory of Ultra-Coarse-Graining. 2. Numerical Implementation

Aram Davtyan, James F. Dama, Anton V. Sinitskiy, Gregory A. Voth [The University of Chicago]

J. Chem. Theor. and Comp., **10**, 5265–5275, 2014.

The increasing interest in the modeling of complex macromolecular systems in recent years has spurred the development of numerous coarse-graining (CG) techniques. However, many of the CG models are constructed assuming that all details beneath the resolution of CG degrees of freedom are fast and average out, which sets limits on the resolution of feasible coarse-grainings and on the range of applications of the CG models. Here, we discuss the UCG methodology and its numerical implementation. We pay particular attention to the numerical mechanism for including state transitions between different conformations within CG sites because this has not been discussed previously.

Surprisal Metrics for Quantifying Perturbed Conformational Dynamics in Markov State Models

Vincent A. Voelz [Temple University, Philadelphia], Brandon Elman, Asghar M. Razavi, Guangfeng Zhou

J. Chem. Theor. and Comp., **10**, 5716–5728, 2014.

Markov state models (MSMs), which model conformational dynamics as a network of transitions between metastable states, have been increasingly used to model the thermodynamics and kinetics of biomolecules. In considering perturbations to molecular dynamics induced by sequence mutations, chemical modifications, or changes in external conditions, it is important to assess how transition rates change, independent of changes in metastable state definitions. Here, we present a surprisal metric to quantify the difference in metastable state transitions for two closely related MSMs, taking into account the statistical uncertainty in observed transition counts.

Protein Conformational Analysis (Cont'd)

Long-Range Conformational Transition of a Photoswitchable Allosteric Protein: Molecular Dynamics Simulation Study

Sebastian Buchenberg, Volker Knecht, Reto Walser, Peter Hamm, Gerhard Stock[University of Freiburg]

J. Phys. Chem. B., **118**, 13468–13476, 2014.

A local perturbation of a protein may lead to functional changes at some distal site. An example is the PDZ2 domain of human tyrosine phosphatase 1E, which shows an allosteric transition upon binding to a peptide ligand. Recently Buchli et al. presented a time-resolved study of this transition by covalently linking an azobenzene photoswitch across the binding groove and using a femtosecond laser pulse that triggers the cis–trans photoisomerization of azobenzene. To aid the interpretation of these experiments, in this work seven microsecond runs of all-atom molecular dynamics simulations each for the wild-type PDZ2 in the ligand-bound and -free state, as well as the photoswitchable protein (PDZ2S) in the cis and trans states of the photoswitch, in explicit water were conducted.

Conformational Behavior of Flavin Adenine Dinucleotide: Conserved Stereochemistry in Bound and Free States

Gopi Kuppuraj [Ochanomizu University,], Dennis Kruise, Kei Yura

J. Phys. Chem. B., **118**, 13486–13497, 2014.

Metabolic enzymes utilize the cofactor flavin adenine dinucleotide (FAD) to catalyze essential biochemical reactions. Because these enzymes have been implicated in disease pathways, it will be necessary to target them via FAD-based structural analogues that can either activate/inhibit the enzymatic activity. To achieve this, it is important to explore the conformational space of FAD in the enzyme-bound and free states. Herein, we analyze X-ray crystallographic data of the enzyme-bound FAD conformations and sample conformations of the molecule in explicit water by molecular dynamics (MD) simulations.

An analysis approach to identify specific functional sites in orthologous proteins using sequence and structural information: Application to neuroserpin reveals regions that differentially regulate inhibitory activity

Tet Woo Lee[University of Auckland], Annie Shu-Ping Yang, Thomas Brittain, Nigel P. Birch

Proteins: Stru. Fun. & Bioinf., **83**, 135–152, 2015.

The analysis of sequence conservation is commonly used to predict functionally important sites in proteins. We have developed an approach that first identifies highly conserved sites in a set of orthologous sequences using a weighted substitution-matrix-based conservation score and then filters these conserved sites based on the pattern of conservation present in a wider alignment of sequences from the same family and structural information to identify surface-exposed sites. This allows us to detect specific functional sites in the target protein and exclude regions that are likely to be generally important for the structure or function of the wider protein family.

Protein Structure Analysis

Effect of Hydrophobic Interactions on the Folding Mechanism of β -Hairpins

Alexander Popp, Ling Wu, Timothy A. Keiderling
[University of Illinois at Chicago], Karin Hauser

J. Phys. Chem. B., **118**, 14234–14242, 2014.

Hydrophobic interactions are essential in stabilizing protein structures. How they affect the folding pathway and kinetics, however, is less clear. We used time-resolved infrared spectroscopy to study the dynamics of hydrophobic interactions of β -hairpin variants of the sequence Trpzip2 (SWTWENGKWTWK-NH₂) that is stabilized by two cross-strand Trp–Trp pairs. The hydrophobicity strength was varied by substituting the tryptophans pairwise by either tyrosines or valines. Relaxation dynamics were induced by a laser-excited temperature jump, which separately probed for the loss of the cross-strand β -hairpin interaction and the rise of the disordered structure.

mAb806 binding to epidermal growth factor receptor: a computational study

Yao Zong Ng, Srinivasaraghavan Kannan, David P. Lane, Gloria Fuentes, Chandra S. Verma [Bioinformatics Institute (A*STAR)]

Proteins: Stru. Fun. & Bioinf., **83**, 153–168, 2015.

The epidermal growth factor receptor (EGFR) is an important target in the treatment of cancer. A very potent antibody, mAb806, has been developed against overexpressed EGFR and was found to be particularly active in brain tumors. Structural studies reveal that it binds to an epitope on the extracellular region of the EGFR. However, this epitope is cryptic/buried in crystal structures of the active (untethered) and inactive (tethered) EGFR, and it is unclear as to how the antibody interacts with this region. To explore this interaction, we combined molecular docking, steered molecular dynamics, and equilibrium molecular dynamics simulations.

Protein Dynamics

Mechanisms of Differential Allosteric Modulation in Homologous Proteins: Insights from the Analysis of Internal Dynamics and Energetics of PDZ Domains

Giulia Morra, Alessandro Genoni, Giorgio Colombo [Istituto di Chimica del Riconoscimento Molecolare]

J. Chem. Theor. and Comp., **10**, 5677–5689, 2014.

Allostery is a general phenomenon in proteins whereby a perturbation at one site reverberates into a functional change at another one, through modulation of its conformational dynamics. Herein, we address the problem of how the molecular signal encoded by a ligand is differentially transmitted through the structures of two homologous PDZ proteins: PDZ2, which responds to binding with structural and dynamical changes in regions distal from the ligand site, and PDZ3, which is characterized by less-intense dynamical variations. We use novel methods of analysis of MD simulations in the unbound and bound states to investigate the determinants of the differential allosteric behavior of the two proteins.

Protein Dynamics (Cont'd)

Reactive Molecular Dynamics Study of the pH-Dependent Dynamic Structure of α -Helix

M. Golkaram, Y. K. Shin, A. C. T. van Duin [The Pennsylvania State University]

J. Phys. Chem. B., **118**, 13498–13504, 2014.

We have studied the α -helix to random coil transition using ReaxFF reactive molecular dynamics as a function of pH. Urea binding to peptides and associated interference with backbone H-bonds and charged side chains interactions, which can both denature the helices, have been studied previously using nonreactive force fields (Topol, I. A. J. Am. Chem. Soc. 2001, 123, 6054–6060). This study reveals new proton-transfer mechanisms related to the denaturation of α -helical structures, which cannot be captured by nonreactive molecular dynamics.

Effects of Macromolecular Crowding on Amyloid Beta (16–22) Aggregation Using Coarse-Grained Simulations

David C. Latshaw, Mookyung Cheon, Carol K. Hall [North Carolina State University]

J. Phys. Chem. B., **118**, 13513–13526, 2014.

To examine the effect of crowding on protein aggregation, discontinuous molecular dynamics (DMD) simulations combined with an intermediate resolution protein model, PRIME20, were applied to a peptide/crowder system. The systems contained 192 A β (16–22) peptides and crowders of diameters 5, 20, and 40 Å, represented here by simple hard spheres, at crowder volume fractions of 0.00, 0.10, and 0.20. Results show that both crowder volume fraction and crowder diameter have a large impact on fibril and oligomer formation. Results show that both crowder volume fraction and crowder diameter have a large impact on fibril and oligomer formation. surface area increases.

Induced Ice Melting by the Snow Flea Antifreeze Protein from Molecular Dynamics Simulations

Guido Todde, Christopher Whitman, Sven Hovmöller, Aatto Laaksonen [Stockholm University]

J. Phys. Chem. B., **118**, 13527–13534, 2014.

Antifreeze proteins (AFP) allow different life forms, insects as well as fish and plants, to survive in subzero environments. AFPs prevent freezing of the physiological fluids. We have studied, through molecular dynamics simulations, the behavior of the small isoform of the AFP found in the snow flea (sfAFP), both in water and at the ice/water interface, of four different ice planes. In water at room temperature, the structure of the sfAFP is found to be slightly unstable. The loop between two polyproline II helices has large fluctuations as well as the C-terminus.

Interactions of Urea with Native and Unfolded Proteins: A Volumetric Study

Ikbae Son, Yuen Lai Shek, Anna Tikhomirova, Eduardo Hidalgo Baltasar, Tigran V. Chalikian [University of Toronto]

J. Phys. Chem. B., **118**, 13554–13563, 2014.

We describe a statistical thermodynamic approach to analyzing urea-dependent volumetric properties of proteins. We use this approach to analyze our urea-dependent data on the partial molar volume and adiabatic compressibility of lysozyme, apocytochrome c, ribonuclease A, and α -chymotrypsinogen A. The analysis produces the thermodynamic properties of elementary urea–protein association reactions while also yielding estimates of the effective solvent-accessible surface areas of the native and unfolded protein states. Lysozyme and apocytochrome c do not undergo urea-induced transitions.

Ligand Binding/Docking

β -Lactam Estrogen Receptor Antagonists and a Dual-Targeting Estrogen Receptor/Tubulin Ligand

Niamh M. O'Boyle, Jade K. Pollock, Miriam Carr, Andrew J. S. Knox, Seema M. Nathwani, Shu Wang, Laura Caboni, Daniela M. Zisterer, Mary J. Meegan[Trinity Biomedical Sciences Institute]

J.Med.Chem., **57**, 9370–9382, 2014.

Twelve novel β -lactams were synthesized and their antiproliferative effects and binding affinity for the predominant isoforms of the estrogen receptor (ER), ER α and ER β , were determined. β -Lactams 23 and 26 had the strongest binding affinities for ER α (IC₅₀ values: 40 and 8 nM, respectively) and ER β (IC₅₀ values: 19 and 15 nM). β -Lactam 26 was the most potent in antiproliferative assays using MCF-7 breast cancer cells, and further biochemical analysis showed that it caused accumulation of cells in G2/M phase (mitotic blockade) and depolymerization of tubulin in MCF-7 cells.

Predicted 3D structures of olfactory receptors with details of odorant binding to OR1G1

Soo-Kyung Kim, William A. Goddard III[California Institute of Technology]

J.Comp.Aided. Mol.des. **28**, 1175-1190, 2014.

Olfactory receptors (ORs) are responsible for mediating the sense of smell; they allow humans to recognize an enormous number of odors but the connection between binding and perception is not known. We predict the ensemble of low energy structures for the human OR1G1 (hOR1G1) and also for six other diverse ORs, using the G protein-coupled receptor Ensemble of Structures in Membrane BiLayer Environment complete sampling method that samples 13 trillion different rotations and tilts using four different templates to predict the 24 structures likely to be important in binding and activation.

Role of Desolvation in Thermodynamics and Kinetics of Ligand Binding to a Kinase

Jagannath Mondal, Richard A. Friesner, and B. J. Berne [Columbia University]

J. Chem. Theor. and Comp. **10**, 5696–5705, 2014.

Computer simulations are used to determine the free energy landscape for the binding of the anticancer drug Dasatinib to its src kinase receptor and show that before settling into a free energy basin the ligand must surmount a free energy barrier. An analysis based on using both the ligand-pocket separation and the pocket-water occupancy as reaction coordinates shows that the free energy barrier is a result of the free energy cost for almost complete desolvation of the binding pocket. The simulations further show that the barrier is not a result of the reorganization free energy of the binding pocket.

Survey of phosphorylation near drug binding sites in the Protein Data Bank (PDB) and their effects

Kyle P. Smith, Kathleen M. Gifford, Joshua S. Waitzman, Sarah E. Rice[Northwestern University Feinberg School of Medicine]

Proteins: Stru. Fun. & Bioinf., **83**, 25–36, 2015.

While it is currently estimated that 40 to 50% of eukaryotic proteins are phosphorylated, little is known about the frequency and local effects of phosphorylation near pharmaceutical inhibitor binding sites. In this study, we investigated how frequently phosphorylation may affect the binding of drug inhibitors to target proteins. We examined the 453 non-redundant structures of soluble mammalian drug target proteins bound to inhibitors currently available in the Protein Data Bank (PDB). We cross-referenced these structures with phosphorylation data available from the PhosphoSitePlus database.

Ligand Binding / Docking (Cont'd)

Examination of polypeptide substrate specificity for *Escherichia coli* ClpB

Tao Li, Jiabei Lin, Aaron L. Lucius [The University of Alabama at Birmingham]

Proteins: Stru. Fun. & Bioinf., **83**, 117–134, 2015.

Escherichia coli ClpB is a molecular chaperone that belongs to the Clp/Hsp100 family of AAA+ proteins. ClpB is able to form a hexameric ring structure to catalyze protein disaggregation with the assistance of the DnaK chaperone system. Our knowledge of the mechanism of how ClpB recognizes its substrates is still limited. We have quantitatively investigated ClpB binding to a number of unstructured polypeptides using steady-state anisotropy titrations. To precisely determine the binding affinity for the interaction between ClpB hexamers and polypeptide substrates the titration data were subjected to global non-linear least squares analysis incorporating the dynamic equilibrium of ClpB assembly.

Enzyme Catalysis

Protein Isotope Effects in Dihydrofolate Reductase From *Geobacillus stearothermophilus* Show Entropic–Enthalpic Compensatory Effects on the Rate Constant

Louis Y. P. Luk, J. Javier Ruiz-Pernía, William M. Dawson, E. Joel Loveridge, Iñaki Tuñón, Vicent Moliner, Rudolf K. Allemann [Cardiff University]

J. Am. Chem. Soc., 2013, **136**, 17317–17323, 2014.

Catalysis by dihydrofolate reductase from the moderately thermophilic bacterium *Geobacillus stearothermophilus* (BsDHFR) was investigated by isotope substitution of the enzyme. The enzyme kinetic isotope effect for hydride transfer was close to unity at physiological temperatures but increased with decreasing temperatures to a value of 1.65 at 5 °C. This behavior is opposite to that observed for DHFR from *Escherichia coli* (EcDHFR), where the enzyme kinetic isotope effect increased slightly with increasing temperature. These experimental results were reproduced in the framework of variational transition-state theory that includes a dynamical recrossing coefficient that varies with the mass of the protein.

Analysis of Subpocket Selectivity and Identification of Potent Selective Inhibitors for Matriptase and Matriptase-2

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J. Med. Chem., **57**, 10198–10204, 2014.

We studied the factors affecting the selectivity of peptidomimetic inhibitors of the highly homologous proteases matriptase and matriptase-2 across subpockets using docking simulations. We observed that the farther away a subpocket is located from the catalytic site, the more pronounced its role in selectivity. As a result of our exhaustive virtual screening, we biochemically validated novel potent and selective inhibitors of both enzymes.

A QM/MM study of the associative mechanism for the phosphorylation reaction catalyzed by protein kinase A and its D166A mutant

Ayax Pérez-Gallegos, Mireia Garcia-Viloca, Àngels González-Lafont [Universitat Autònoma de Barcelona], José M. Lluch

J. Comp. Aided. Mol. des. **28**, 1077–1091, 2014.

Here we analyze in detail the possible catalytic role of the associative mechanism in the γ -phosphoryl transfer reaction in the catalytic subunit of the mammalian cyclic AMP-dependent protein kinase (PKA) enzyme and its D166A mutant. We have used a complete solvated model of the ATP-Mg₂-Kemptide/PKA system and good levels of theory (B3LYP/MM and MP2/MM) to determine several potential energy paths from different MD snapshots, and we present a deep analysis of the interaction distances and energies between ligands, metals and enzyme residues.

Enzyme Catalysis (Cont'd)

Structure–Function Analysis of the Conserved Tyrosine and Diverse π -Stacking among Class I Histone Deacetylases: A QM (DFT)/MM MD Study

Jingwei Zhou, Hujun Xie, Zhihong Liu, Hai-Bin Luo[Sun Yat-sen University], Ruibo Wu

J.Chem. Infor. and Mod. **54**, 3162–3171, 2014.

Discovery of the isoform-selective histone deacetylases (HDACs) inhibitors is of great medical importance and still a challenge. The comparison studies on the structure–function relationship of the conserved residues, which are located in the linker binding channel among class I HDACs (including 4 isoforms: HDAC1/2/3/8), have been carried out by using ab initio QM/MM MD simulations, a state-of-the-art approach to simulate metallo-enzymes. We found that the conserved tyrosine (Y303/308/286/306 in HDAC1/2/3/8, respectively) could modulate the zinc-inhibitor chelation among all class I HDACs with different regulatory mechanisms.

Ab Initio QM/MM Study Shows a Highly Dissociated SN2 Hydrolysis Mechanism for the cGMP-Specific Phosphodiesterase-5

Zhe Li, Yinuo Wu, Ling-Jun Feng, Ruibo Wu[Sun Yat-Sen University], Hai-Bin Luo

J. Chem. Theor. and Comp. **10**, 5448–5457, 2014.

Phosphodiesterases (PDEs) are the sole enzymes hydrolyzing the important second messengers cGMP and cAMP and have been identified as therapeutic targets for several diseases. The most successful examples are PDE5 inhibitors (i.e., sildenafil and tadalafil), which have been approved for the treatment of male erectile dysfunction and pulmonary hypertension. However, the side effects mostly due to nonselective inhibition toward other PDE isoforms, set back the clinical usage of PDE5 inhibitors. Herein, the first computational study on the catalytic hydrolysis mechanism of cGMP for PDE5 (catalytic domain) is performed by employing the state-of-the-art ab initio quantum mechanics/molecular mechanics (QM/MM) molecular dynamics (MD) simulations.

Catalytic Mechanism of Retroviral Integrase for the Strand Transfer Reaction Explored by QM/MM Calculations

Ana R. Araújo, António J. M. Ribeiro, Pedro A. Fernandes, Maria J. Ramos [Universidade do Porto]

J. Chem. Theor. and Comp. **10**, 5458–5466, 2014.

Integrase (IN) is one of the three fundamental enzymes for the HIV life cycle. It irreversibly inserts the viral DNA into the host DNA, infecting the host cells. Although there are 37 compounds currently used in the HIV-1 antiretroviral therapy, only three have IN as a target. Lack of structural and mechanistic information on IN greatly contributes to such a small number. Recently, the crystal structure of the PFV intasome became available, which allowed us to perform accurate high-level quantum mechanics/molecular mechanics (QM/MM) calculations to determine the strand transfer reaction mechanism followed by IN.

Enzyme Catalysis (Cont'd)

Multiscale Simulations Give Insight into the Hydrogen In and Out Pathways of [NiFe]-Hydrogenases from *Aquifex aeolicus* and *Desulfovibrio fructosovorans*

Francesco Oteri, Marc Baaden, Elisabeth Lojou, Sophie Sacquin-Mora [Institut de Biologie Physico-Chimique]

J. Phys. Chem. B., **118**, 13800–13811, 2014.

[NiFe]-hydrogenases catalyze the cleavage of molecular hydrogen into protons and ELECTRONS and represent promising tools for H₂-based technologies such as biofuel cells. However, many aspects of these enzymes remain to be understood, in particular how the catalytic center can be protected from irreversible inactivation by O₂. In this work, we combined homology modeling, all-atom molecular dynamics, and coarse-grain Brownian dynamics simulations to investigate and compare the dynamic and mechanical properties of two [NiFe]-hydrogenases: the soluble O₂-sensitive enzyme from *Desulfovibrio fructosovorans*, and the O₂-tolerant membrane-bound hydrogenase from *Aquifex aeolicus*.

Catalytic Activity of Human Placental Alkaline Phosphatase (PLAP): Insights from a Computational Study

Gabriela L. Borosky [Universidad Nacional de Córdoba]

J. Phys. Chem. B., **118**, 14302–14313, 2014.

Alkaline phosphatases (APs) catalyze the hydrolysis and transphosphorylation of phosphate monoesters. Quantum-mechanical computational methods were employed to study the catalytic mechanism of human placental AP (PLAP). An active-site model was used, constructed on the basis of the X-ray crystal structure of the enzyme. Kinetic and thermodynamic evaluations were achieved for each reaction step. Calculations shed light on the mechanistic differences that had been experimentally observed between aryl and alkyl phosphates, particularly regarding the rate-determining step.

Computational Investigation of Glycosylase and β -Lyase Activity Facilitated by Proline: Applications to FPG and Comparisons to hOgg1

Shahin Sowlati-Hashjin , Stacey D. Wetmore [University of Lethbridge]

J. Phys. Chem. B., **118**, 14566–14577, 2014.

Quantum mechanical methods are used to investigate the chemical steps during the bifunctional (glycosylase and β -lyase) activity of bacterial FPG DNA glycosylase, which removes the major oxidation product (8-oxoguanine) from DNA as part of the base excision repair process. To facilitate investigation of all potential pathways, the smallest chemically relevant model is implemented, namely a modified OG nucleoside-3'-monophosphate and a truncated proline nucleophile. Potential energy surfaces are characterized with SMD-M06-2X/6-311+G(2df,2p)/PCM-B3LYP/6-31G(d) and compared to a previous study on the analogues human enzyme (hOgg1), which uses a lysine nucleophile.

A QM/MM study of the reaction mechanism of (R)-hydroxynitrile lyases from *Arabidopsis thaliana* (AtHNL)

Wenyou Zhu, Yongjun Liu [Shandong University] , Rui Zhang

Proteins: Stru. Fun. & Bioinf., **83**, 66–77, 2015.

Hydroxynitrile lyases (HNLs) catalyze the conversion of chiral cyanohydrins to hydrocyanic acid (HCN) and aldehyde or ketone. Hydroxynitrile lyase from *Arabidopsis thaliana* (AtHNL) is the first R-selective HNL enzyme containing an α/β -hydrolases fold. In this article, the catalytic mechanism of AtHNL was theoretically studied by using QM/MM approach based on the recently obtained crystal structure in 2012. Two computational models were constructed, and two possible reaction pathways were considered.

Enzyme Catalysis (Cont'd)

Role of active-site residues Tyr55 and Tyr114 in catalysis and substrate specificity of *Corynebacterium diphtheriae* C-S lyase

Alessandra Astegno [University of Verona], Alessandra Allegrini, Stefano Piccoli, Alejandro Giorgetti, Paola Dominici

Proteins: Stru. Fun. & Bioinf., **83**, 78–90, 2015.

In recent years, there has been increased interest in bacterial methionine biosynthesis enzymes as antimicrobial targets because of their pivotal role in cell metabolism. C-S lyase from *Corynebacterium diphtheriae* is a pyridoxal 5'-phosphate-dependent enzyme in the transsulfuration pathway that catalyzes the α,β -elimination of sulfur-containing amino acids, such as L-cystathionine, to generate ammonia, pyruvate, and homocysteine, the immediate precursor of L-methionine. In order to gain deeper insight into the functional and dynamic properties of the enzyme, mutants of two highly conserved active-site residues, Y55F and Y114F, were characterized by UV-visible absorbance, fluorescence, and CD spectroscopy in the absence and presence of substrates and substrate analogs, as well as by steady-state kinetic studies.

Protein-Protein Interactions

Pepper: cytoscape app for protein complex expansion using protein–protein interaction networks

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Bioinformatics. **30**, 3419–3420, 2014.

We introduce PEPPER (Protein complex Expansion using Protein–Protein intERactions), a Cytoscape app designed to identify protein complexes as densely connected subnetworks from seed lists of proteins derived from proteomic studies. PEPPER identifies connected subgraph by using multi-objective optimization involving two functions: (i) the coverage, a solution must contain as many proteins from the seed as possible, (ii) the density, the proteins of a solution must be as connected as possible, using only interactions from a proteome-wide interaction network.

Protein–protein binding affinity prediction from amino acid sequence

K. Yugandhar, M. Michael Gromiha[Indian Institute of Technology Madras]

Bioinformatics. **30**, 3583–3589, 2014.

Protein–protein interactions play crucial roles in many biological processes and are responsible for smooth functioning of the machinery in living organisms. Predicting the binding affinity of protein–protein complexes provides deep insights to understand the recognition mechanism and identify the strong binding partners in protein–protein interaction networks. In this work, we have collected the experimental binding affinity data for a set of 135 protein–protein complexes and analyzed the relationship between binding affinity and 642 properties obtained from amino acid sequence.

Protein-Protein Interactions (Cont'd)

Asymmetric Binding to NS5A by Daclatasvir (BMS-790052) and Analogs Suggests Two Novel Modes of HCV Inhibition

James H. Nettles [Emory University School of Medicine], Richard A. Stanton, Joshua Broyde, Franck Amblard, Hongwang Zhang, Longhu Zhou, Junxing Shi, Tamara R. McBrayer, Tony Whitaker, Steven J. Coats, James J. Kohler, and Raymond F. Schinazi

J.Med.Chem., **57**, 10031–10043, 2014.

Symmetric, dimeric daclatasvir (BMS-790052) is the clinical lead for a class of picomolar inhibitors of HCV replication. While specific, resistance-bearing mutations at positions 31 and 93 of domain I strongly suggest the viral NS5A as target, structural mechanism(s) for the drugs' activities and resistance remains unclear. Several previous models suggested symmetric binding modes relative to the homodimeric target; however, none can fully explain SAR details for this class. We present semiautomated workflows to model potential receptor conformations for docking.

Investigation of the intermolecular recognition mechanism between the E3 ubiquitin ligase Keap1 and substrate based on multiple substrates analysis

Zheng-Yu Jiang, Li-Li Xu, Meng-Chen Lu, Yang Pan, Hao-Ze Huang, Xiao-Jin Zhang, Hao-Peng Sun, Qi-Dong You [China Pharmaceutical University]

J.Comp.Aided. Mol.des. **28**, 1233-1245, 2014.

E3 ubiquitin ligases are attractive drug targets due to their specificity to the ubiquitin machinery. However, the development of E3 ligase inhibitors has proven challenging for the fact that they must disrupt protein–protein interactions (PPIs). The E3 ligase involved in interactome provide new hope for the discovery of the E3 ligase inhibitors. These currently known natural binding partners of the E3 ligase can benefit the discovery of other unknown substrates and also the E3 ligase inhibitors. Herein, we present a novel strategy that using multiple substrates to elucidate the molecular recognition mechanism of E3 ubiquitin ligase.

Which Three-Dimensional Characteristics Make Efficient Inhibitors of Protein–Protein Interactions?

Méline A. Kuenemann, Laura M. L. Bourbon, Céline M. Labbé, Bruno O. Villoutreix, Olivier Sperandio [Université Paris Diderot]

J.Chem. Infor. and Mod. **54**, 3067–3079, 2014.

The specific properties of protein–protein interactions (PPI) (flat, large and hydrophobic) make them harder to tackle with low-molecular-weight compounds. Learning from the properties of successful examples of PPI interface inhibitors (iPPI) at earlier stages of developments, has been pinpointed as a powerful strategy to circumvent this trend. To this end, we have computationally analyzed the bioactive conformations of iPPI and those of inhibitors of conventional targets (e.g enzymes) to highlight putative iPPI 3D characteristics.

Membrane Proteins and Lipid Peptide Interactions

AFAL: a web service for profiling amino acids surrounding ligands in proteins

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J.Comp.Aided. Mol.des. **28**, 1069-1076, 2014.

With advancements in crystallographic technology and the increasing wealth of information populating structural databases, there is an increasing need for prediction tools based on spatial information that will support the characterization of proteins and protein–ligand interactions. Herein, a new web service is presented termed amino acid frequency around ligand (AFAL) for determining amino acids type and frequencies surrounding ligands within proteins deposited in the [Protein Data Bank](#) and for assessing the atoms and atom–ligand distances involved in each interaction.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Exploring the dynamics and interaction of a full ErbB2 receptor and Trastuzumab-Fab antibody in a lipid bilayer model using Martini coarse-grained force field

Juan Felipe Franco-Gonzalez, Javier Ramos, Victor L. Cruz [Instituto de Estructura de la Materia], Javier Martinez-Salazar

J.Comp.Aided. Mol.des. **28**, 1093-1107, 2014.

Coarse grained (CG) modeling has been applied to study the influence of the Trastuzumab monoclonal antibody on the structure and dynamics of the full ErbB2 receptor dimer, including the lipid bilayer. The usage of CG models to study such complexes is almost mandatory, at present, due to the large size of the whole system. We will show that the Martini model performs satisfactorily well, giving results well-matched with those obtained by atomistic models as well as with the experimental information existing on homolog receptors.

Extraction of Protein Binding Pockets in Close Neighborhood of Bound Ligands Makes Comparisons Simple Due to Inherent Shape Similarity

Timo Krotzky, Thomas Rickmeyer, Thomas Fober, Gerhard Klebe [University of Marburg]

J.Chem. Infor. and Mod. **54**, 3229–3237, 2014.

Methods for comparing protein binding sites are frequently validated on data sets of pockets that were obtained simply by extracting the protein area next to the bound ligands. With this strategy, any unoccupied pocket will remain unconsidered. Furthermore, a large amount of ligand-biased intrinsic shape information is predefined, inclining the subsequent comparisons as rather trivial even in data sets that hardly contain redundancies in sequence information. In this study, we present the results of a very simplistic and shape-biased comparison approach, which stress that unrestricted cavity extraction is essential to enable unexpected cross-reactivity predictions among proteins and function annotations of orphan proteins.

Treatment of Ionic Strength in Biomolecular Simulations of Charged Lipid Bilayers

Diogo Vila-Viçosa, Vitor H. Teixeira, Hugo A. F. Santos, António M. Baptista, Miguel Machuqueiro [Universidade de Lisboa]

J. Chem. Theor. and Comp. **10**, 5483–5492, 2014.

Biological membranes are complex systems that have recently attracted a significant scientific interest. Due to the presence of many different anionic lipids, these membranes are usually negatively charged and sensitive to pH. The protonation states of lipids and the ion distribution close to the bilayer are two of the main challenges in biomolecular simulations of these systems. In this work, we propose a method based on the Poisson–Boltzmann equation to estimate the counterion and co-ion concentration close to a lipid bilayer that avoids the need for neutrality at this microscopic level.

Accelerating All-Atom MD Simulations of Lipids Using a Modified Virtual-Sites Technique

Bastien Loubet, Wojciech Kopec, Himanshu Khandelia [University of Southern Denmark]

J. Chem. Theor. and Comp. **10**, 5690–5695, 2014.

We present two new implementations of the virtual sites technique which completely suppresses the degrees of freedom of the hydrogen atoms in a lipid bilayer allowing for an increased time step of 5 fs in all-atom simulations of the CHARMM36 force field. One of our approaches uses the derivation of the virtual sites used in GROMACS while the other uses a new definition of the virtual sites of the CH₂ groups. Our methods is tested on a DPPC (no unsaturated chain), a POPC (one unsaturated chain), and a DOPC (two unsaturated chains) lipid bilayers.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Reparameterized United Atom Model for Molecular Dynamics Simulations of Gel and Fluid Phosphatidylcholine Bilayers

Richard Tjörnhammar ,Olle Edholm[AlbaNova University Center]

J. Chem. Theor. and Comp., **10**, 5706–5715, 2014.

A new united atom parametrization of diacyl lipids like dipalmitoylphosphatidylcholine (DPPC) and the dimyristoylphosphatidylcholine (DMPC) has been constructed based on ab initio calculations to obtain fractional charges and the dihedral potential of the hydrocarbon chains, while the Lennard-Jones parameters of the acyl chains were fitted to reproduce the properties of liquid hydrocarbons. The results have been validated against published experimental X-ray and neutron scattering data for fluid and gel phase DPPC. The derived charges of the lipid phosphatidylcholine (PC) headgroup are shown to yield dipole components in the range suggested by experiments.

Dynamics of Lipids, Cholesterol, and Transmembrane α -Helices from Microsecond Molecular Dynamics Simulations

Michelle K. Baker , Cameron F. Abrams [Drexel University]

J. Phys. Chem. B., **118**, 13590–13600, 2014.

Extensive all-atom molecular dynamics ($\sim 24 \mu\text{s}$ total) allowed exploration of configurational space and calculation of lateral diffusion coefficients of the components of a protein-embedded, cholesterol-containing model bilayer. The three model membranes are composed of an $\sim 50/50$ (by mole) dipalmitoylphosphatidylcholine (DPPC)/cholesterol bilayer and contained an α -helical transmembrane protein (HIV-1 gp41 TM). Despite the high concentration of cholesterol, normal Brownian motion was observed and the calculated diffusion coefficients (on the order of $10\text{--}9 \text{ cm}^2/\text{s}$) are consistent with experiments.

Effect of Methyl-Branched Fatty Acids on the Structure of Lipid Bilayers

David Poger [The University of Queensland], Bertrand Caron, Alan E. Mark

J. Phys. Chem. B., **118**, 13838–13848, 2014.

Methyl-branched fatty acids are widespread in prokaryotic membranes. Although anteiso and iso branching (that is on the antepenultimate and penultimate carbons) and the presence of multiple methyl branches in the phytanoyl chain are known to modify the thermotropic behavior and enhance the fluidity of lipid bilayers, little is known about the effect of methyl branching on the structure of lipid bilayers. In this study, molecular dynamics simulations are used to examine systematically the impact of one or more methyl branches at different positions along the sn-1 palmitoyl chain on the structural properties of a 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) lipid bilayer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Interplay of LNA and 2'-O-Methyl RNA in the Structure and Thermodynamics of RNA Hybrid Systems: A Molecular Dynamics Study Using the Revised AMBER Force Field and Comparison with Experimental Results

Ilyas Yildirim [Northwestern University], Elzbieta Kierzek, Ryszard Kierzek, George C. Schatz

J. Phys. Chem. B., **118**, 14177–14187, 2014.

When used in nucleic acid duplexes, locked nucleic acid (LNA) and 2'-O-methyl RNA residues enhance the duplex stabilities, and this makes it possible to create much better RNA aptamers to target specific molecules in cells. Thus, LNA and 2'-O-methyl RNA residues are finding increasingly widespread use in RNA-based therapeutics. We utilize MD simulations and UV melting experiments to investigate the structural and thermodynamic properties of 13 nucleic acid duplexes, including full DNA, RNA, LNA, and 2'-O-methyl RNA duplexes as well as hybrid systems such as LNA:RNA, 2'-O-methyl RNA:RNA, LNA/2'-O-methyl RNA:RNA, and RNA/2'-O-methyl RNA:RNA duplexes.

Understanding Thermal Phases in Atomic Detail by All-Atom Molecular-Dynamics Simulation of a Phospholipid Bilayer

Koji Ogata [RIKEN Innovation Center], Waka Uchida, Shinichiro Nakamura

J. Phys. Chem. B., **118**, 14353–14365, 2014.

All-atom molecular dynamics (MD) simulations were used to investigate the thermal phase behavior of two hydrated phospholipids, namely, DPPC and DPPE, at the atomic level. The trajectories in the MD simulations clearly identified the structures of DPPC in the crystalline (Lc), gel (Lβ), ripple (Pβ), and liquid-crystalline (Lα) phases and those of DPPE in the Lc and Lα phases. The physicochemical and structural properties of these phases agree well with the experimental results.

Relevant Interactions of Antimicrobial Iron Chelators and Membrane Models Revealed by Nuclear Magnetic Resonance and Molecular Dynamics Simulations

João T. S. Coimbra, Tânia Moniz, Natércia F. Brás, Galya Ivanova, Pedro A. Fernandes, Maria J. Ramos, Maria Rangel [Universidade do Porto]

J. Phys. Chem. B., **118**, 14590–14601, 2014.

The dynamics and interaction of 3-hydroxy-4-pyridinone fluorescent iron chelators, exhibiting antimicrobial properties, with biological membranes were evaluated through NMR and molecular dynamics simulations. Both NMR and MD simulation results support a strong interaction of the chelators with the lipid bilayers that seems to be strengthened for the rhodamine containing compounds, in particular for compounds that include ethyl groups and a thiourea link. For the latter type of compounds the interaction reaches the hydrophobic core of the lipid bilayer.

Protein Folding

Protein folding pathways extracted by OFLOOD: Outlier FLOODing method

Ryuhei Harada, Tomotake Nakamura, Yu Takano, Yasuteru Shigeta [University of Tsukuba]

J. Comp. Chem., **36**, 97–102, 2015.

The Outlier FLOODing method (OFLOOD) is proposed as an efficient conformational sampling method to extract biologically rare events such as protein folding. In OFLOOD, sparse distributions (outliers in the conformational space) were regarded as relevant states for the transitions. Then, the transitions were enhanced through conformational resampling from the outliers. This evidence indicates that the conformational resampling of the sparse distributions might increase chances for promoting the transitions from the outliers to other meta-stable states, which resembles a conformational flooding from the outliers to the neighboring clusters.

Protein-Nucleic acid Interactions

Structure–activity relationships of thiostrepton derivatives: implications for rational drug design

Antje Wolf, Sebastian Schoof, Sascha Baumann, Hans-Dieter Arndt, Karl N. Kirschner [Bonn-Rhein-Sieg University of Applied Sciences]

J.Comp.Aided. Mol.des. **28**, 1205–1215, 2014.

The bacterial ribosome is a major target of naturally occurring thiopeptides antibiotics. Studying thiopeptide (e.g. thiostrepton) binding to the GAR's 23S·L11 ribosomal subunit using docking methods is challenging. Regarding the target, the binding site is composed of a flexible protein–RNA nonbonded interface whose available crystal structure is of medium resolution. Regarding the ligands, the thiopeptides are chemically complex, flexible, and contain macrocycles. In this study we developed a combined MD–docking–MD workflow that allows us to study thiopeptide–23S·L11 binding.

Nucleic Acid Quadruplexes Based on 8-Halo-9-deazaxanthines: Energetics and Noncovalent Interactions in Quadruplex Stems

Yevgen P. Yurenko, Jan Novotný, Mariusz P. Mitoraj, Vladimír Sklenář, Artur Michalak, Radek Marek [Masaryk University]

J. Chem. Theor. and Comp. **10**, 5353–5365, 2014.

Structural and energetic features of artificial DNA quadruplexes consisting of base tetrads and their stacks with Na⁺/K⁺ ion(s) inside the central pore and incorporating halogenated derivatives of xanthine, 8-fluoro-9-deazaxanthine (FdaX), 8-chloro-9-deazaxanthine (CldaX), 8-bromo-9-deazaxanthine (BrdaX), or 8-iodo-9-deazaxanthine (IdaX), have been investigated by modern state-of-the-art computational tools. The DNA (or RNA) quadruplex models based on 8-halo-9-deazaxanthines are predicted to be more stable relative to those with unmodified xanthine due to the increased stabilizing contributions coming from all three main types of weak interactions (H-bonding, stacking, and ion coordination).

Cy3 and Cy5 Dyes Terminally Attached to 5'C End of DNA: Structure, Dynamics, and Energetics

Ondřej Kroutil, Ingrid Romancová, Miroslav Šíp, Zdeněk Chval [University of South Bohemia]

J. Phys. Chem. B., **118**, 13564–13572, 2014.

Cy3 and Cy5 cyanine dyes terminally attached to the 5'C end (C1) of the DNA oligonucleotide were studied by metadynamics (MTD), molecular dynamics (MD), and density-functional methods with dispersion corrections (DFT-D). MTD simulations explored the free energy surface (FES) of the dye–DNA interactions, which included stacking and major groove binding motifs and unstacked structures. Dynamics of the stacked structures was studied by the MD simulations. All possible combinations of stacking interactions between the two indole rings of the dyes and the neighbor guanine and cytosine rings were observed.

Nucleic Acids

PrEMeR-CG: inferring nucleotide level DNA methylation values from MethylCap-seq data

David E. Frankhouser, Mark Murphy, James S. Blachly, Jincheol Park, Mike W. Zoller, Javkhlan-Ochir Ganbat, John Curfman, John C. Byrd, Shili Lin, Guido Marcucci, Pearly Yan, Ralf Bundschuh[The Ohio State University]

Bioinformatics. **30**, 3567-3574, 2014.

DNA methylation is an epigenetic change occurring in genomic CpG sequences that contribute to the regulation of gene transcription both in normal and malignant cells. Next-generation sequencing has been used to characterize DNA methylation status at the genome scale, but suffers from high sequencing cost in the case of whole-genome bisulfite sequencing, or from reduced resolution (inability to precisely define which of the CpGs are methylated) with capture-based techniques. Here we present a computational method that computes nucleotide-resolution methylation values from capture-based data by incorporating fragment length profiles into a model of methylation analysis.

Expected degree for RNA secondary structure networks

Peter Clote[Boston College]

J. Comp. Chem., **36**, 103–117, 2015.

Consider the network of all secondary structures of a given RNA sequence, where nodes are connected when the corresponding structures have base pair distance one. The expected degree of the network is the average number of neighbors, where average may be computed with respect to the either the uniform or Boltzmann probability. Here, we describe the first algorithm, **RNAexpNumNbors**, that can compute the expected number of neighbors, or expected network degree, of an input sequence. For RNA sequences from the Rfam database, the expected degree is significantly less than the constrained minimum free energy structure, defined to have minimum free energy (MFE) over all structures consistent with the Rfam consensus structure.

Surfaces, Catalysts and Materials Subjects

Molecular Dynamics Simulations Reveal a Dielectric-Responsive Coronal Structure in Protein-Polymer Surfactant Hybrid Nanoconstructs

Alex P. S. Brogan, Richard B. Sessions, Adam W. Perriman, Stephen Mann [University of Bristol]

J. Am. Chem. Soc., 2013, **136**, 16824–16831, 2014.

Solvent-free liquid proteins are a new class of thermally stable hybrid bionanomaterials that are produced by extensive lyophilization of aqueous solutions of protein-polymer surfactant nanoconjugates followed by thermal annealing. The hybrid constructs, which consist of a globular protein core surrounded by a monolayer of electrostatically coupled polymer surfactant molecules, exhibit nativelike structure, function, and backbone dynamics over a large temperature range. We present molecular dynamics simulations of protein-polymer surfactant nanoconjugates consisting of globular cores of myoglobin or lysozyme and demonstrate that the derived structural parameters are highly consistent with experimental values.

Surfaces, Catalysts and Material Subjects (Cont'd)

Toward a Materials Genome Approach for Ionic Liquids: Synthesis Guided by Ab Initio Property Maps

Fangyong Yan, Michael Lartey, Kuldeep Jariwala, Sage Bowser, Krishnan Damodaran, Erik Albenze, David R. Luebke, Hunaid B. Nulwala, Berend Smit, Maciej Haranczyk [Lawrence Berkeley National Laboratory]

J. Phys. Chem. B., **118**, 13609–13620, 2014.

The Materials Genome Approach (MGA) aims to accelerate development of new materials by incorporating computational and data-driven approaches to reduce the cost of identification of optimal structures for a given application. Here, we use the MGA to guide the synthesis of triazolium-based ionic liquids (ILs). Our approach involves an IL property-mapping tool, which merges combinatorial structure enumeration, descriptor-based structure representation and sampling, and property prediction using molecular simulations.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Development and implementation of (Q)SAR modeling within the CHARMMing web-user interface

Iwona E. Weidlich [Computational Drug Design Systems (CODDES) LLC], Yuri Pevzner, Benjamin T. Miller, Igor V. Filippov, H. Lee Woodcock, Bernard R. Brooks

J. Comp. Chem., **36**, 62–67, 2015.

Recent availability of large publicly accessible databases of chemical compounds and their biological activities (PubChem, ChEMBL) has inspired us to develop a web-based tool for structure activity relationship and quantitative structure activity relationship modeling to add to the services provided by CHARMMing (www.charmming.org). This new module implements some of the most recent advances in modern machine learning algorithms—Random Forest, Support Vector Machine, Stochastic Gradient Descent, Gradient Tree Boosting, so forth.

Quantile regression model for a diverse set of chemicals: application to acute toxicity for green algae

Jonathan Villain, Sylvain Lozano, Marie-Pierre Halm-Lemeille, Gilles Durrieu, Ronan Bureau [Normandie University]

J. Mol.Mod., **20**, 2508, 2014.

The potential of quantile regression (QR) and quantile support vector machine regression (QSVMR) was analyzed for the definitions of quantitative structure-activity relationship (QSAR) models associated with a diverse set of chemicals toward a particular endpoint. This study focused on a specific sensitive endpoint (acute toxicity to algae) for which even a narcosis QSAR model is not actually clear. An initial dataset including more than 401 ecotoxicological data for one species of algae (*Selenastrum capricornutum*) was defined.

Quantitative Structure-Activity Relations (Cont'd)

Benchmarking Study of Parameter Variation When Using Signature Fingerprints Together with Support Vector Machines

Jonathan Alvarsson [Uppsala University], Martin Eklund, Claes Andersson, Lars Carlsson, Ola Spjuth, and Jarl E. S. Wikberg

J.Chem. Infor. and Mod. **54**, 3211–3217, 2014.

QSAR modeling using molecular signatures and support vector machines with a radial basis function is increasingly used for virtual screening in the drug discovery field. This method has three free parameters: C , γ , and signature height. C is a penalty parameter that limits overfitting, γ controls the width of the radial basis function kernel, and the signature height determines how much of the molecule is described by each atom signature. Determination of optimal values for these parameters is time-consuming. The goal of this project was to investigate whether such default values could be found by using seven public QSAR data sets spanning a wide range of end points and using both a bit version and a count version of the molecular signatures.

Potentials and Parameters

A comparison between parallelization approaches in molecular dynamics simulations on GPUs

Lorenzo Rovigatti [Sapienza—Università di Roma], Petr Šulc, István Z. Reguly, Flavio Romano

J. Comp. Chem., **36**, 1–8, 2015.

We test the relative performances of two different approaches to the computation of forces for molecular dynamics simulations on graphics processing units. A “vertex-based” approach, where a computing thread is started per particle, is compared to an “edge-based” approach, where a thread is started per each potentially non-zero interaction. We find that the former is more efficient for systems with many simple interactions per particle while the latter is more efficient if the system has more complicated interactions or fewer of them.

Paramfit: Automated optimization of force field parameters for molecular dynamics simulations

Robin M. Betz, Ross C. Walker [Department of Chemistry and Biochemistry, UC San Diego]

J. Comp. Chem., **36**, 79–87, 2015.

The generation of bond, angle, and torsion parameters for classical molecular dynamics force fields typically requires fitting parameters such that classical properties such as energies and gradients match precalculated quantum data for structures that scan the value of interest. We present a program, Paramfit, distributed as part of the AmberTools software package that automates and extends this fitting process, allowing for simplified parameter generation for applications ranging from single molecules to entire force fields.

Unbinding Pathways of VEGFR2 Inhibitors Revealed by Steered Molecular Dynamics

Anna Maria Capelli, Gabriele Costantino [Università degli Studi di Parma]

J.Chem. Infor. and Mod. **54**, 3124–3136, 2014.

A detailed atomistic description of the unbinding process of sorafenib and sunitinib, two known VEGFR2 inhibitors clinically used to treat renal cell carcinoma, was unraveled by using steered molecular dynamics (SMD) simulations. While sunitinib is a fast-dissociating binder, sorafenib exhibits quite a long residence time at this enzyme, which might impact its duration of action in vivo. In order to gain insights into the kinetically different behaviors of the two inhibitors, an SMD study was carried out, which involved a careful optimization of the force and velocity parameters.

Potentials and Parameters (Cont'd)

Automatic Selection of Order Parameters in the Analysis of Large Scale Molecular Dynamics Simulations

Mohammad M. Sultan, Gert Kiss, Diwakar Shukla, Vijay S. Pande [Stanford University]

J. Chem. Theor. and Comp., **10**, 5217–5223, 2014.

Given the large number of crystal structures and NMR ensembles that have been solved to date, classical MD simulations have become powerful tools in the atomistic study of the kinetics and thermodynamics of biomolecular systems on ever increasing time scales. By virtue of the high-dimensional conformational state space that is explored, the interpretation of large-scale simulations faces difficulties not unlike those in the big data community. We address this challenge by introducing a method, clustering based feature selection (CB-FS) that employs a posterior analysis approach.

Molecular Dynamics

Structural Insights into Trapping and Dissociation of Small Molecules in K⁺ Channels

Tobias Linder, Priyanka Saxena, Eugen Timin, Steffen Hering, Anna Strydom [University of Vienna]

J. Chem. Infor. and Mod., **54**, 3218–3228, 2014.

K⁺ channels play a critical role in numerous physiological and pathophysiological processes rendering them an attractive target for therapeutic intervention. However, the hERG K⁺ channel poses a special challenge in drug discovery, since block of this channel by a plethora of diverse chemical entities can lead to long QT syndrome and sudden death. Of particular interest is the so-called trapping phenomenon, characterized by capture of a drug behind closed channel gates, which harbors an increased pro-arrhythmic risk. In this study we investigated the influence of trapped blockers on the gating dynamics and probed the state dependence of dissociation in K⁺ channels by making use of the quaternary tetrabutylammonium.

Optical Signature of Formation of Protein Corona in the Firefly Luciferase-CdSe Quantum Dot Complex

Jennifer M. Elward, Flaviyan Jerome Irudayanathan, Shikha Nangia, Arindam Chakraborty [Aberdeen Proving Ground]

J. Chem. Theor. and Comp., **10**, 5224–5228, 2014.

Theoretical investigation of protein corona is challenging because of the size of the protein-dot complex. In this work, we have addressed this computational bottleneck by combining pseudopotential + explicitly correlated Hartree–Fock QM calculations with molecular mechanics, molecular dynamics, and Monte Carlo techniques. The optical gap of a 5 nm CdSe quantum dot (Cd1159Se1183) was computed by sequential addition of luciferase (Lu), and a red shift of 8 nm in the λ_{max} of protein corona (CdSe–Lu7) was observed.

Diabatic Population Matrix Formalism for Performing Molecular Mechanics Style Simulations with Multiple Electronic States

Jae Woo Park, Young Min Rhee [Pohang University of Science and Technology (POSTECH)]

J. Chem. Theor. and Comp., **10**, 5238–5253, 2014.

An accurate description of nonbonded interactions is important in investigating dynamics of molecular systems. In many situations, fixed point charge models are successfully applied to explaining various chemical phenomena. However, these models with conventional formulations will not be appropriate in elucidating the detailed dynamics during nonadiabatic events. This is mainly because the chemical properties of any molecule, especially its ELECTRONIC populations, significantly change with respect to molecular distortions in the vicinity of the surface crossing.

Molecular Dynamics (Cont'd)

Effect of Uranyl Ion Concentration on Structure and Dynamics of Aqueous Uranyl Solution: A Molecular Dynamics Simulation Study

Manish Chopra , Niharendu Choudhury [Bhabha Atomic Research Centre]

J. Phys. Chem. B., **118**, 14373–14381, 2014.

The effect of uranyl ion concentration on structure and dynamics of aqueous solutions of uranyl ions is investigated by molecular dynamics simulations. In order to get an idea about the effect of concentration of uranyl ions on local structural arrangements of water molecules around the uranyl ion, radial distribution functions of water molecules around the uranyl ion are analyzed for aqueous uranyl solutions of various concentrations. The concentration effect on translational dynamics has also been analyzed by calculating diffusion coefficients of uranyl ion, water, and nitrate ions in solution from their respective mean squared displacements.

Monte Carlo

Constant pressure hybrid Monte Carlo simulations in GROMACS

Mario Fernández-Pendás, Bruno Escribano [Basque Center for Applied Mathematics], Tijana Radivojević, Elena Akhmatskaya

J. Mol.Mod., **20**, 2487, 2014.

Adaptation and implementation of the Generalized Shadow Hybrid Monte Carlo (GSHMC) method for molecular simulation at constant pressure in the NPT ensemble are discussed. The resulting method, termed NPT-GSHMC, combines Andersen barostat with GSHMC to enable molecular simulations in the environment natural for biological applications, namely, at constant pressure and constant temperature. Generalized Hybrid Monte Carlo methods are designed to maintain constant temperature and volume and extending their functionality to preserving pressure is not trivial.

QM and QM/MM

Computing pK_A values of hexa-aqua transition metal complexes

Gegham Galstyan , Ernst-Walter Knapp[Freie Universität Berlin]

J. Comp. Chem., **36**, 69–78, 2015.

Aqueous pK_A values for 15 hexa-aqua transition metal complexes were computed using a combination of quantum chemical and electrostatic methods. Two different structure models were considered optimizing the isolated complexes in vacuum or in presence of explicit solvent using a QM/MM approach. They yield very good agreement with experimentally measured pK_A values with an overall root mean square deviation of about 1 pH unit, excluding a single but different outlier for each of the two structure models. These outliers are hexa-aqua Cr(III) for the vacuum and hexa-aqua Mn(III) for the QM/MM structure model.

QM and QM/MM (Cont'd)

Understanding the cytotoxicity or cytoprotective effects of biological and synthetic quinone derivatives by redox mechanism

Rosivaldo S. Borges[Universidade Federal do Pará], Agnaldo S. Carneiro, Tainá G. Barros, Carlos A. L. Barros, Antonio M. J. Chaves Neto, Albérico B. F. da Silva

J. Mol.Mod., **20**, 2541, 2014.

Quinones represent an important class of biological compounds, but are also involved with toxicological intermediates and among their hazardous effects include cytotoxicity, immunotoxicity, and carcinogenesis. The structure–toxicity relationship for quinone derivatives has been used to cytotoxicity or cytoprotective effects by redox mechanism is determined using quantum chemical calculations through the density functional theory (DFT). According to our DFT study, the ELECTRON acceptance is related with LUMO, electron affinity, and stabilization energy values.

A density functional reactivity theory (DFRT) based approach to understand the interaction of cisplatin analogues with protecting agents

Amrit Sarmah, Ram Kinkar Roy[Birla Institute of Technology and Science (BITS)]

J.Comp.Aided. Mol.des. **28**, 1153-1173, 2014.

In the present study some new insights are put into one of the major concern of cisplatin therapy and that is on the reduction of various cytotoxic and nephrotoxic side-effects of cisplatin analogues in cancer treatment. A better understanding of the interaction between different cisplatin analogues with various protecting agents can be achieved from the descriptors generated by density functional reactivity theory based comprehensive decomposition analysis of stabilization energy (Bagaria et al. in Phys Chem Chem Phys 11:8306–8315, 2009) scheme.

Toward On-The-Fly Quantum Mechanical/Molecular Mechanical (QM/MM) Docking: Development and Benchmark of a Scoring Function

Prasad Chaskar, Vincent Zoete [Swiss Institute of Bioinformatics], Ute F. Röhrig

J.Chem. Infor. and Mod. **54**, 3137–3152, 2014.

We address the challenges of treating polarization and covalent interactions in docking by developing a hybrid quantum mechanical/molecular mechanical (QM/MM) scoring function based on the semiempirical self-consistent charge density functional tight-binding (SCC-DFTB) method and the CHARMM force field. To benchmark this scoring function within the EADock DSS docking algorithm, we created a publicly available dataset of high-quality X-ray structures of zinc metalloproteins (<http://www.molecular-modelling.ch/resources.php>).

Local Hybrid QM/QM Calculations of Reaction Pathways in Metallobiosites

Milica Andrejić ,Ricardo A. Mata [Georg-August-Universität Göttingen]

J. Chem. Theor. and Comp. **10**, 5397–5404, 2014.

The accurate calculation of activation barriers is fundamental for the modeling of reaction pathways. However, the computational cost of describing ELECTRONIC correlation at metal sites can be a deterrent. We present calculations on two selected molybdenum complexes modeling the active sites of sulfite oxidase and dimethyl sulfoxide reductase. Use is made of the LMOMO scheme, a hybrid QM/QM model that enables the partition of the system directly at the orbital level, thus avoiding the use of model systems. The results show that even when the high-level calculations are restricted to the orbitals directly located at the metal atom, most of the electronic correlation effects are captured.

Comparative or Homology Modeling

A Set of Computationally Designed Orthogonal Antiparallel Homodimers that Expands the Synthetic Coiled-Coil Toolkit

Christopher Negron , Amy E. Keating [Massachusetts Avenue, Cambridge]

J. Am. Chem. Soc., 2013, **136**, 16544–16556, 2014.

Molecular engineering of protein assemblies, including the fabrication of nanostructures and synthetic signaling pathways, relies on the availability of modular parts that can be combined to give different structures and functions. Currently, a limited number of well-characterized protein interaction components are available. Coiled-coil interaction modules have been demonstrated to be useful for biomolecular design, and many parallel homodimers and heterodimers are available in the coiled-coil toolkit. In this work, we sought to design a set of orthogonal antiparallel homodimeric coiled coils using a computational approach.

Ligand Docking

Predicting peptide binding sites on protein surfaces by clustering chemical interactions

Chengfei Yan , Xiaoqin Zou[University of Missouri]

J. Comp. Chem., **36**, 49–61, 2015.

Short peptides play important roles in cellular processes including signal transduction, immune response, and transcription regulation. Correct identification of the peptide binding site on a given protein surface is of great importance not only for mechanistic investigation of these biological processes but also for therapeutic development. In this study, we developed a novel computational approach, referred to as ACCLUSTER, for predicting the peptide binding sites on protein surfaces. Specifically, we use the 20 standard amino acids as probes to globally scan the protein surface.

Fast Identification of Novel Lymphoid Tyrosine Phosphatase Inhibitors Using Target–Ligand Interaction-Based Virtual Screening

Xuben Hou, Rong Li, Kangshuai Li, Xiao Yu, Jin-Peng Sun [Shandong University] , and Hao Fang

J. Med. Chem., **57**, 9309–9322, 2014.

Lymphoid-specific tyrosine phosphatase (Lyp), a critical signaling regulator of immune cells, is associated with various autoimmune diseases, including type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus. Recent research suggests that Lyp is a potential drug target for autoimmune diseases. Herein, we applied a target–ligand interaction-based virtual screening method to identify novel Lyp inhibitors. Nine Lyp inhibitors with novel scaffolds were identified with eight reversible inhibitors (K_i values ranged from 2.87 to 28.03 μM) and one covalent inhibitor ($K_i = 40.98 \pm 13.19 \mu\text{M}$).

Ligand Docking (Cont'd)

Dynamic characterization and substrate binding of cis-2,3-dihydrobiphenyl-2,3-diol dehydrogenase—an enzyme used in bioremediation

Stefano Piccoli, Francesco Musiani, Alejandro Giorgetti
[University of Verona]

J. Mol.Mod., **20**, 2531, 2014.

In recent years, techniques involving the use of organisms to remove or neutralize pollutants from contaminated sites have attracted great attention. The aim of bioremediation is to use naturally occurring organisms to degrade dangerous substances to less toxic or non toxic molecules. The gram-negative bacterium *Pandora* *pnumenusa* strain B-356 (Pp) has been found to be able to transform a persistent class of organic pollutant compounds, namely the biphenyl and polychlorinated biphenyls (PCBs). A key enzyme in the PCB catabolic pathway is NAD-dependent cis-2,3-dihydrobiphenyl-2,3-diol dehydrogenase (BphB), for which the crystal structure from Pp has been crystallized in apo-, NAD-bound and biphenyldiol-/NAD-bound forms.

Exploring the interactions between isoprenoid chain and labdenediol diphosphate synthase based on molecular docking and quartz crystal microbalance

Wujun Liu [Dalian Institute of Chemical Physics], Wei Yang, Yixin Zhang, Zongbao Kent Zhao

J. Mol.Mod., **20**, 2527, 2014.

Many natural PRODUCTS and biosynthetic intermediates contain isoprenoid chains. Isoprenoid chains are believed to interact with some proteins in the biological systems, but such interactions remain poorly understood. Here labdenediol diphosphate synthase (LPPS) was used as a model to explore the molecular interactions involving isoprenoid chains. Both homology modeling and docking simulation results indicated that binding form between isoprenoid chain and LPPS is dominated by hydrophobic forces in one binding site. The interactions were also examined via quartz crystal microbalance (QCM) technology using synthetic isoprenoid chain-contained probes.

Seeking potential anticonvulsant agents that target GABA_A receptors using experimental and theoretical procedures

Margarita Virginia Saavedra-Vélez, José Correa-Basurto, Myrna H. Matus, Eloy Gasca-Pérez, Martiniano Bello, Roberto Cuevas-Hernández, Rosa Virginia García-Rodríguez, José Trujillo-Ferrara, Fernando Rafael Ramos-Morales [Universidad Veracruzana]

J.Comp.Aided. Mol.des. **28**, 1217-1232, 2014.

The aim of this study was to identify compounds that possess anticonvulsant activity by using a pentylenetetrazol (PTZ)-induced seizure model. Theoretical studies of a set of ligands, explored the binding affinities of the ligands for the GABA_A receptor (GABA_AR), including some benzodiazepines. The ligands satisfy the Lipinski rules and contain a pharmacophore core that has been previously reported to be a GABA_AR activator. To select the ligands with the best physicochemical properties, all of the compounds were analyzed by quantum mechanics and the energies of the highest occupied molecular orbital and lowest unoccupied molecular orbital were determined.

Ligand Docking (Cont'd)

Extended Template-Based Modeling and Evaluation Method Using Consensus of Binding Mode of GPCRs for Virtual Screening

Miwa Sato , Takatsugu Hirokawa [National Institute of Advanced Industrial Science and Technology (AIST)]

J.Chem. Infor. and Mod. **54**, 3153–3161, 2014.

G-protein-coupled receptors (GPCRs) are a pharmaceutically important protein family because they mediate numerous physiological functions. The crystal structures of several GPCR subtypes have been determined recently, encouraging efforts to apply structure-based virtual screening (SBVS) along with ligand-based virtual screening (LBVS) to improve the hit rate of active ligands from large chemical libraries. Three-dimensional models are also necessary for GPCR targets whose structures are unknown. Current challenges include the selection of structural templates from available structurally known GPCRs to use for accurate modeling and understanding the diversity of sites recognizing distinct ligands.

Docking Ligands into Flexible and Solvated Macromolecules. 7. Impact of Protein Flexibility and Water Molecules on Docking-Based Virtual Screening Accuracy

Eric Therrien, Nathanael Weill, Anna Tomberg, Christopher R. Corbeil, Devin Lee, Nicolas Moitessier [McGill University]

J.Chem. Infor. and Mod. **54**, 3198–3210, 2014.

The use of predictive computational methods in the drug discovery process is in a state of continual growth. Over the last two decades, an increasingly large number of docking tools have been developed to identify hits or optimize lead molecules through in-silico screening of chemical libraries to proteins. In recent years, the focus has been on implementing protein flexibility and water molecules. Our efforts led to the development of FITTED first reported in 2007 and further developed since then. In this study, we wished to evaluate the impact of protein flexibility and occurrence of water molecules on the accuracy of the FITTED docking program to discriminate active compounds from inactive compounds in virtual screening (VS) campaigns.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 36 (1), January, 2015.

- 1–8 **A comparison between parallelization approaches in molecular dynamics simulations on GPUs**, Lorenzo Rovigatti [Sapienza—Università di Roma], Petr Šulc, István Z. Reguly, Flavio Romano

See Methodology / Potentials and Parameters.

- 9–21 **A comprehensive DFT investigation of bulk and low-index surfaces of ZrO₂ polymorphs**, Chiara Ricca, Armelle Ringuedé, Michel Cassir, Carlo Adamo, Frederic Labat [Institut de Recherche de Chimie de Paris]

The bulk structure, the relative stability, and the ELECTRONIC properties of monoclinic, tetragonal, and cubic ZrO₂ have been studied from a theoretical point of view, through periodic ab initio calculations using different Gaussian basis sets together with Hartree–Fock (HF), pure Density Functional Theory (DFT), and mixed HF/DFT schemes as found in hybrid functionals.

- 22–32 **From orientation disordered to ordered—An *ab initio* simulation on ammonia borane phase transition within van der Waals corrections**, Qi Song, Zhenyi Jiang, Zhiyong Zhang [Northwest University], Yuqing Hou, Xiaodong Zhang

In this work, we report a detailed theoretical investigation of the phase transition of ammonia borane (NH₃BH₃; AB), from a tetragonal *I*4mm(*C*_{4v}) phase with disordered orientation of hydrogen to an orthorhombic phase with *P*mn2₁(*C*_{2v}) symmetry, as a function of temperature based on Density Functional Theory calculations with semiempirical dispersion potential correction.

- 33–41 **Prediction of the reduction potential of tris(2,2'-bipyridinyl)iron(III/II) derivatives**, Hyungjun Kim, Joungwon Park, Yoon Sup Lee[KAIST]

The reduction potentials of a tris(2,2'-bipyridinyl)iron (III/II) and iron(III/II) couples complexed with 2,2'-bipyridinyl derivatives in acetonitrile are predicted using density functional theory. The calculation protocol proposed by Kim et al. (Kim, J. Park, Y. S. Lee, J. Comput. Chem. 2013, 34, 2233) showing reliable performance for the reduction potential is used.

- 42–48 **1,2-migration in *N*-phosphano functionalized *N*-heterocyclic carbenes**, Andrey A. Kirilchuk, Aleksandr A. Yurchenko, Aleksandr N. Kostyuk, Alexander B. Rozhenko[National Academy of Sciences of Ukraine]

1,2-Migration of the phosphano-group to the carbene center in *N*-phosphano functionalized *N*-heterocyclic carbenes has been studied by density functional theory (DFT) calculations.

- 49–61 **Predicting peptide binding sites on protein surfaces by clustering chemical interactions**, Chengfei Yan, Xiaoqin Zou[University of Missouri]

See Methodology / Ligand Docking.

- 62–67 **Development and implementation of (Q)SAR modeling within the CHARMMing web-user interface**, Iwona E. Weidlich [Computational Drug Design Systems (CODDES) LLC], Yuri Pevzner, Benjamin T. Miller, Igor V. Filippov, H. Lee Woodcock, Bernard R. Brooks

See Methodology / QSAR.

Journal of Computational Chemistry, 36 (2), January, 2015.

- 69–78 **Computing pK_A values of hexa-aqua transition metal complexes**, Gegham Galstyan, Ernst-Walter Knapp [Freie Universität Berlin]

See Methodology / QM and QM/MM.

- 79–87 **Paramfit: Automated optimization of force field parameters for molecular dynamics simulations**, Robin M. Betz, Ross C. Walker [Department of Chemistry and Biochemistry, UC San Diego]

See Methodology / Potentials and Parameters.

- 88–96 **A systematic study of rare gas atoms encapsulated in small fullerenes using dispersion corrected density functional theory**, Rebecca Sure [Massey University Auckland], Ralf Tonner, Peter Schwerdtfeger

The most stable fullerene structures from C_{20} to C_{60} are chosen to study the energetics and geometrical consequences of encapsulating the rare gas elements He, Ne, or Ar inside the fullerene cage using dispersion corrected density functional theory. An exponential increase in stability is found with increasing number of carbon atoms.

- 97–102 **Protein folding pathways extracted by OFLOOD: Outlier FLOODing method**, Ryuhei Harada, Tomotake Nakamura, Yu Takano, Yasuteru Shigeta [University of Tsukuba]

See Applications / Protein Folding.

- 103–117 **Expected degree for RNA secondary structure networks**, Peter Clote [Boston College]

See Applications / Nucleic Acids.

- 118–128 **How does hybrid bridging core modification enhance the nonlinear optical properties in donor- π -acceptor configuration? A case study of dinitrophenol derivatives**, Shabbir Muhammad [King Khalid University], Ahmad Irfan, Mohd Shkir, Aijaz R. Chaudhry, Abul Kalam, Salem AlFaify, Abdullah G. Al-Sehemi, A. E. Al-Salami, I. S. Yahia, Hong-Liang Xu, Zhong-Min Su

This study spotlights the fundamental insights about the structure and static first hyperpolarizability (β) of a series of 2,4-dinitrophenol derivatives (1–5), which are designed by novel bridging core modifications. The central bridging core modifications show noteworthy effects to modulate the optical and nonlinear optical properties in these derivatives.

- 129–135 **Hybrid MPI/OpenMP parallelization of the effective fragment potential method in the *libefp* software library**, Ilya A. Kaliman, Lyudmila V. Slipchenko [Purdue University]

A new hybrid MPI/OpenMP parallelization scheme is introduced for the Effective Fragment Potential (EFP) method implemented in the *libefp* software library. The new implementation employs dynamic load balancing algorithm that uses a master/slave model.

Journal of Molecular Modeling, 20 (12), December, 2014.

- 2549 **Ground- and excited-state stability of the conformers of 3,5-dinitrocatechol and its complexes with W(VI) and V(V): combined theoretical and experimental study**, V. B. Delchev [University of Plovdiv], K. B. Gavazov, I. G. Shterev

The investigation showed that irradiation of DNC is accompanied by a parallel proton migration from the hydroxy group to the neighboring NO₂ group, which results in a large Stokes shift of the absorption and emission bands.

- 2547 **How does the increment of hetero-cyclic conjugated moieties affect electro-optical and charge transport properties of novel naphtha-difuran derivatives? A computational approach**, Aijaz Rasool Chaudhry [Universiti Teknologi Malaysia], R. Ahmed, Ahmad Irfan, Shabbir Muhammad, A. Shaari, Abdullah G. Al-Sehemi

We have investigated computationally the effects of π -conjugation extension on naphtha[2,1-b:6,5-b'] difuran (DPNDF); where we increase the number of fused NDF (central core) and furan rings in the parent molecule.

- 2545 **An ab initio study on the concerted interaction between chalcogen and pnictogen bonds**, Bahman Mohammadian Asiabar, Mehdi D. Esrafil [University of Maragheh], Fariba Mohammadian-Sabet, Hamid Reza Sobhi, Majid Javaheri

We analyzed cooperation between chalcogen-bonding and pnictogen-bonding interactions in XHS...NCH₂P...NCY (X = F, Cl; Y = H, OH, NH₂, CN and NC) complexes at the MP2/6–311++G** level. These effects were studied in terms of geometric and energetic properties, harmonic frequencies, and nuclear magnetic resonance (NMR).

- 2543 **A DFT study on surface dependence of β -Ga₂O₃ for CO₂ hydrogenation to CH₃OH**, Jin Qu, Shik Chi Edman Tsang, Xue-Qing Gong [East China University of Science and Technology]

In this paper, the catalytic activities of various β -Ga₂O₃ surfaces for CO₂ hydrogenation have been studied by density functional theory (DFT) calculations.

- 2541 **Understanding the cytotoxicity or cytoprotective effects of biological and synthetic quinone derivatives by redox mechanism**, Rosivaldo S. Borges [Universidade Federal do Pará], Agnaldo S. Carneiro, Tainá G. Barros, Carlos A. L. Barros, Antonio M. J. Chaves Neto, Albérico B. F. da Silva

See Methodology / QM and QM/MM.

- 2539 **Functionalization of the pristine and stone-wales defected BC3 graphenes with pyrene**, Ali Ahmadi Peyghan[Islamic Azad University], Maziar Noei, Zargham Bagheri

The functionalization of pristine and Stone-Wales defected BC3 nanosheets with a pyrene molecule was investigated using density functional theory.

- 2538 **Aromaticity, response, and nonlinear optical properties of sumanene modified with boron and nitrogen atoms**, Stevan Armaković [University of Novi Sad], Sanja J. Armaković, Jovan P. Šetrajčić, Vladimir Holodkov

We investigated the effects of substitution on the sumanene benzylic CH₂ groups with BH and NH groups using density functional theory computations. Our study shows that various properties of sumanene could be finely tuned for the application in the areas closely related to the materials science.

- 2537 **Structure, vibrational, and optical properties of platinum cluster: a density functional theory approach**, Ngangbam Bedamani Singh, Utpal Sarkar [Assam University]

Using density functional theory, stability, chemical, and optical properties of small platinum clusters, Pt_n (n = 2 to 10) have been investigated. An attempt has been made to establish a correlation between stability and chemical reactivity parameters.

- 2536 **The structure, stability, and electronic properties of ultra-thin BC₂N nanotubes: a first-principles study**, Yue Wang, Juan Zhang, Gang Huang, Xinhua Yao, Qingyi Shao [South China Normal University]

Rapid developments of the silicon electronics industry have close to the physical limits and nanotube materials are the ideal materials to replace silicon for the preparation of next generation ELECTRONIC devices. Boron-carbon-nitrogen nanotubes (BCNNT) can be formed by joining carbon nanotube (CNT) and boron nitride nanotube (BNNT) segments, and BC₂N nanotubes have been widely and deeply studied.

- 2535 **Optoelectronic and nonlinear optical properties of triarylamine helicenes: a DFT study**, Nasarul Islam, Altaf Hussain Pandith[University of Kashmir]

This work involved the design of a new series of triarylaminehelicenes (TAH) with significant hole transport capacity and enhanced nonlinear optical response. The geometries, ELECTRONIC properties and nonlinear response of TAH derivatives were studied using density functional theory at the B3PW91/6-311++G (2d, 2p) level.

- 2534 **Role of size and shape selectivity in interaction between gold nanoclusters and imidazole: a theoretical study**, Muthuramalingam Prakash, Gilberte Chambaud, M. Mogren Al-Mogren, Majdi Hochlaf [Université Paris-Est]

We present a theoretical study on the structure, stability, spectra and ELECTRONIC properties of imidazole (Im) adsorbed on GOLD nanoclusters (Au_n, n = 2, 4, 6, 8, 10, and 20). These computations were performed using various density functional theories with and without inclusion of Grimme's (D3) dispersion correction.

- 2533 **Computational evaluation of unsaturated carbonitriles as neutral receptor model for beryllium(II) recognition**, Ahmad Nazmi Rosli [University of Malaya], Mohd Rais Ahmad, Yatimah Alias, Sharifuddin Md Zain, Vannajan Sanghiran Lee, Pei Meng Woi

Design of neutral receptor molecules (ionophores) for beryllium(II) using unsaturated carbonitrile models has been carried out via density functional theory, G3, and G4 calculations.

- 2532 **A theoretical investigation of one-dimensional lithium-bonded chain: enhanced first hyperpolarizability and little red-shift**, Fang Ma[Huaibei Normal University], Dongsheng Bai, Hongliang Xu

We present a theoretical investigation of the electric properties of two kinds of one-dimensional lithium bonded chains: (NC-Li) $_n$ and (NC-CC-Li) $_n$ ($n = 1-8$). The resulting (NC-Li) $_n$ and (NC-CC-Li) $_n$ were found to exhibit enhanced first hyperpolarizabilities (β) with increasing n , and a slight change in the absorption maximum wavelength λ_{max} at the crucial transition.

- 2531 **Dynamic characterization and substrate binding of cis-2,3-dihydrobiphenyl-2,3-diol dehydrogenase—an enzyme used in bioremediation**, Stefano Piccoli, Francesco Musiani, Alejandro Giorgetti [University of Verona]

See Methodology / Ligand Docking.

- 2530 **Combined effect of confinement and affinity of crowded environment on conformation switching of adenylate kinase**, Min Li, Weixin Xu, John Z. H. Zhang [East China Normal University], Fei Xia

The actual conformation switching of proteins in the crowded cellular environment is completely different from that in vitro. Proteins in cytoplasm are continually subject to confinement and/or attraction to other molecules in their surroundings due to the existence of various biological species. To gain insight into the nature of crowded environments, we investigated the effects of confinement and affinity on the conformation switching of adenylate kinase (ADK) in a spherical cavity.

- 2529 **Computational studies of intermolecular interactions in aqueous solutions of poly(vinylmethylether)**, J. Saramak, K. Halagan, M. Kozanecki [Lodz University of Technology], P. Polanowski

Thermo-responsive materials, such as poly(vinylmethylether) (PVME), attract a common attention because of their unique physical properties resulted from metastable equilibrium between various types of interactions. In this work Monte Carlo (MC) and quantum-mechanical (QM) methods were used to study excluded volume and electrostatic interactions respectively.

- 2528 **Density functional theory calculations insight to the effect of anion on the nonlinear optical properties of LiInX₂ (X = S, Se)**, Fanjie Kong [Yancheng Institute of Technology], Yiliang Liu, Yanfei Hu, Haijun Hou, Feng Hu

The linear and nonlinear optical susceptibilities for LiInS₂ and LiInSe₂ are studied by density functional theory using total energy pseudo potential plane wave method. The structure, band structure, density of states, and frequency-dependent complex dielectric function $\epsilon(\omega)$ are calculated.

- 2527 **Exploring the interactions between isoprenoid chain and labdenediol diphosphate synthase based on molecular docking and quartz crystal microbalance**, Wujun Liu [Dalian Institute of Chemical Physics], Wei Yang, Yixin Zhang, Zongbao Kent Zhao

See Methodology / Ligand Docking.

- 2526 **Synthesis, characterization, and computational study of a new dimethoxy-chalcone**, Ricardo R. Ternavisk, Ademir J. Camargo, Francisco B. C. Machado, José A. F. F. Rocco, Gilberto L. B. Aquino, Valter H. C. Silva, Hamilton B. Napolitano [Universidade Estadual de Goiás]

Chalcones are an important class of medicinal compounds and are known for taking part in various biological activities as in anti-inflammatory, anti-leishmania, antimitotic, and antiviral. Aiming to understand the process of crystal lattice stabilization, a combination of technique has been used including X-ray diffraction, infrared spectroscopy and computational molecular modeling.

- 2524 **An interpretation of the phenol nitration mechanism in the gas phase using G3(MP2)//B3-CEP theory**, Carlos Murilo Romero Rocha [Universidade de Coimbra], José Augusto Rosário Rodrigues, Paulo José Samenho Moran, Rogério Custodio

G3(MP2)//B3-CEP theory was applied to study the mechanism of phenol nitration in the gas phase, as promoted by the electrophile NO_2^+ . The results of studying this mechanism at the G3(MP2)//B3-CEP level pointed to the occurrence of a single-electron transfer (SET) from the aromatic π -system to the nitronium ion prior to σ -complex formation.

- 2523 **Quantum chemical investigation of the primary thermal pyrolysis reactions of the sodium carboxylate group in a brown coal model**, Jian Li, Baisheng Zhang, Zhiqiang Zhang [Taiyuan University of Technology], Kefeng Yan, Lixun Kang

The primary pyrolysis mechanisms of the sodium carboxylate group in sodium benzoate—used as a model compound of brown coal—were studied by performing quantum chemical computations using B3LYP and the CBS method.

- 2522 **Exploratory conformational study of (+)-catechin. Modeling of the polarizability and electric dipole moment**, Erika N. Bentz, Alicia B. Pomilio, Rosana M. Lobayan [Universidad Nacional del Nordeste]

The extension of the study of the conformational space of the structure of (+)-catechin at the B3LYP/6-31G(d,p) level of theory is presented in this paper. (+)-Catechin belongs to the family of the flavan-3-ols, which is one of the five largest phenolic groups widely distributed in nature, and whose biological activity and pharmaceutical utility are related to the antioxidant activity due to their ability to scavenge free radicals.

- 2521 **Theoretical studies on the stability of salts formed by 3-substituted 6-nitraminotetrazines with different cations**, Xueli Zhang, Junqing Yang, Xuedong Gong [Nanjing University of Science and Technology]

A series of energetic salts based on the cations NH_4^+ , NH_3OH^+ , N_2H_5^+ and $\text{C}(\text{NH}_2)_3^+$ and the anions of 6-nitraminotetrazine and its 3-substituted derivatives of $-\text{NH}_2$, $-\text{N}_3$, $-\text{ONO}_2$, $-\text{NF}_2$ or $-\text{NO}_2$ was studied using dispersion-corrected density functional theory (DFT-D).

- 2519 **Theoretical study on the reaction mechanism of chlordimeform with OH radicals**, Shengmin Sun, Kun Zhang, Yang Lu, Hui Zhang [Harbin University of Science and Technology]

A theoretical investigation on the multiple-channel degradation mechanism of chlordimeform with OH radicals in the atmosphere was completed using a dual-level direct dynamics method. The equilibrium geometries and the corresponding harmonic vibrational frequencies of the stationary points were obtained at the M06-2X/6-311++G(d,p) level.

- 2518 **Optimization of selection of chain amine scrubbers for CO₂ capture**, Mohammed J. Al-Marri, Mahmoud M. Khader, Emmanuel P. Giannelis, Mohamed F. Shibl [Qatar University]

In order to optimize the selection of a suitable amine molecule for CO₂ scrubbers, a series of ab initio calculations were performed at the B3LYP/6-31+G(d,p) level of theory. Diethylenetriamine was used as a simple chain amine.

- 2517 **An electro-optical and electron injection study of benzothiazole-based squaraine dyes as efficient dye-sensitized solar cell materials: a first principles study**, Najat Saeed AL-Fahdan, Abdullah M. Asiri, Ahmad Irfan [King Khalid University], Salem A. Basaif, Reda M. El-Shishtawy

Squaraine dyes have attracted significant attention in many areas of daily life from biomedical imaging to semiconducting materials. Moreover, these dyes are used as photoactive materials in the field of solar cells. In the present study, we investigated the structural, electronic, photophysical, and charge transport properties of six benzothiazole-based squaraine dyes (Cis-SQ1–Cis-SQ3 and Trans-SQ1–Trans-SQ3).

- 2516 **Theoretical studies on vicinal-tetrazine compounds: furoxano-1,2,3,4-tetrazine-1,3,5-trioxide (FTTO- α) and furoxano-1,2,3,4-tetrazine-1,3,7-trioxide (FTTO- β)**, Tianyi Wang, Tao Zhang, Liwen Xu, Xionghui Wu, Xuedong Gong, Mingzhu Xia [Nanjing University of Science and Technology]

The derivatives of 1,2,3,4-tetrazine may be promising candidates of high-energy density compounds and are receiving more and more attention. In this study, two 1,2,3,4-tetrazines, furoxano-1,2,3,4-tetrazine-1,3,5-trioxide (FTTO- α) and furoxano-1,2,3,4-tetrazine-1,3,7-trioxide (FTTO- β), were theoretically studied.

- 2514 **Theoretical studies of palladium-catalyzed cycloaddition of alkynyl aryl ethers and alkynes**, Qingxi Meng [Shandong Agricultural University], Fen Wang

Density functional theory (DFT) was used to investigate palladium(0)-catalyzed cycloaddition of alkynyl aryl ethers and alkynes to generate 2-methylidene-2H-chromenes. Calculations indicated that the cycloaddition had five possible reaction pathways: I, II, III, IV, and V.

- 2511 **Calculations of NMR properties for sI and sII clathrate hydrates of methane, ethane and propane**, Paweł Siuda, Joanna Sadlej [University of Warsaw]

Calculations of NMR parameters (the absolute shielding constants and the spin-spin coupling constants) for 512, 51262 and 51264 cages enclathrating CH₄, C₂H₆ and C₃H₈ molecules are presented.

- 2508 **Quantile regression model for a diverse set of chemicals: application to acute toxicity for green algae**, Jonathan Villain, Sylvain Lozano, Marie-Pierre Halm-Lemeille, Gilles Durrieu, Ronan Bureau [Normandie University]

See Methodology / QSAR.

- 2498 **Rovibrational energies and spectroscopic constants for H₂O–Ng complexes**, Wiliam F. da Cunha, Rhuigo Mendes de Oliveira, Luiz F. Roncaratti, João B. L. Martins, Geraldo M. e Silva, Ricardo Gargano [University of Brasilia]

In this work, rovibrational energies and spectroscopic constants for the water –Ng complexes (Ng = He, Ne, Ar, Kr and Xe) were calculated through two different approaches (by solving the Nuclear Schrödinger equation and by applying the Dunham's method) and using two different potential energy curves (PEC).

- 2487 **Constant pressure hybrid Monte Carlo simulations in GROMACS**, Mario Fernández-Pendás, Bruno Escribano [Basque Center for Applied Mathematics], Tijana Radivojević, Elena Akhmatskaya

See Methodology / Monte Carlo.

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About 185 Papers from more than 30 Journals are cited.

1	APPLICATIONS (121)	Page 2		
1.1	Small Molecules (21)			
	General and Model systems	Page 2	Med. Chem. And Drug	Page 3
	Water and Solvation	Page 3	QSAR	Page 7
1.2	Biopolymers (99)			
	Bioinformatics and Cheminformatics	Page 7	Enzyme Catalysis	Page 21
	Comparative or Homology Modeling	Page 11	Protein-Protein Interactions	Page 24
	Protein Conformational Analysis	Page 12	Membrane Proteins	Page 25
	Protein Structure Analysis	Page 13	Protein Folding	Page 29
	Protein Dynamics	Page 15	Protein-Nucleic Acids	Page 30
	Free Energy Calculations	Page 18	Nucleic Acids	Page 31
	Ligand Binding	Page 19		
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 33		
2	METHODOLOGY (45)	Page 33		
	QSAR	Page 33	QM & QM/MM	Page 39
	Potentials and Parameters	Page 34	Comparative or Homology	Page 41
	Molecular Dynamics	Page 35	Ligand Docking	Page 42
	Free Energy Perturbation	Page 38		
3	JOURNAL REVIEWS (8)	Page 46		
	Journal of Molecular Graphics and Modeling, 48 & 49, January & February, 2014.			
	Journal of Computational Chemistry, 35 (2, 3, 4, 5), January & February, 2014.			
	Journal of Molecular Modeling, 20 (1, 2), January & February, 2014			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 60		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

Benchmark Study of the SCC-DFTB Approach for a Biomolecular Proton Channel

Ruibin Liang, Jessica M. J. Swanson, Gregory A. Voth
[University of Chicago]

J. Chem. Theor. and Comp., **10**, 451–462, 2014.

A!

The self-consistent charge density functional tight binding (SCC-DFTB) method has been increasingly applied to study proton transport (PT) in biological environments. However, recent studies revealing some significant limitations of SCC-DFTB for proton and hydroxide solvation and transport in bulk aqueous systems call into question its accuracy for simulating PT in biological systems. The current work benchmarks the SCC-DFTB/MM method against more accurate DFT/MM by simulating PT in a synthetic leucine–serine channel (LS2), which emulates the structure and function of biomolecular proton channels.

Anisotropic Coarse-Grained Model for Proteins Based On Gay–Berne and Electric Multipole Potentials

Hujun Shen, Yan Li, Pengyu Ren, Dinglin Zhang, Guohui Li
[Chinese Academy of Sciences]

J. Chem. Theor. and Comp., **10**, 731–750, 2014.

Gay–Berne anisotropic potential has been widely used to evaluate the nonbonded interactions between coarse-grained particles being described as elliptical rigid bodies. In this paper, we are presenting a coarse-grained model for twenty kinds of amino acids and proteins, based on the anisotropic Gay–Berne and point electric multipole (EMP) potentials. We demonstrate that the anisotropic coarse-grained model, namely GBEMP model, is able to reproduce many key features observed from experimental protein structures (Dunbrack Library), as well as from atomistic force field simulations, while saving the computational cost by a factor of about 10–200 depending on specific cases and atomistic models.



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Water and Solvation

Prediction of Small Molecule Hydration Thermodynamics with Grid Cell Theory

Georgios Gerogiokas, Gaetano Calabro, Richard H. Henchman, Michelle W. Y. Southey, Richard J. Law, Julien Michel [EaStCHEM School of Chemistry]

J. Chem. Theor. and Comp., **10**, 35–48, 2014.

An efficient methodology has been developed to quantify water energetics by analysis of explicit solvent molecular simulations of organic and biomolecular systems. The approach, grid cell theory (GCT), relies on a discretization of the cell theory methodology on a three-dimensional grid to spatially resolve the density, enthalpy, and entropy of water molecules in the vicinity of solute(s) of interest. Entropies of hydration are found to converge more efficiently than enthalpies of hydration.

Dimers of Dimers (DOD): A New Fragment-Based Method Applied to Large Water Clusters

Arjun Saha, Krishnan Raghavachari [Indiana University]

J. Chem. Theor. and Comp., **10**, 58–67, 2014.

We have developed a dimer-based two-body interaction model, denoted “dimers of dimers” (DOD), for the study of water clusters using a fragmentation approach. By including a second layer at a lower level of theory (e.g., Hartree–Fock), our DOD2 model accurately reproduces the total energies of water clusters ranging in size from 16 to 100 molecules using the MP2 method with a variety of basis sets.

Automated Optimization of Water–Water Interaction Parameters for a Coarse-Grained Model

Joseph C. Fogarty, See-Wing Chiu, Peter Kirby, Eric Jakobsson, Sagar A. Pandit [University of South Florida]

J. Phys. Chem. B., **118**, 1603–1611, 2014.

We have developed an automated parameter optimization software framework (ParOpt) that implements the Nelder–Mead simplex algorithm and applied it to a coarse-grained polarizable water model. The model employs a tabulated, modified Morse potential with decoupled short- and long-range interactions incorporating four water molecules per interaction site. Polarizability is introduced by the addition of a harmonic angle term defined among three charged points within each bead.

Medicinal Chemistry and Drug Design

Synthesis, docking simulation, biological evaluations and 3D-QSAR study of 5-Aryl-6-(4-methylsulfonyl)-3-(methylthio)-1,2,4-triazine as selective cyclooxygenase-2 inhibitors

Hamid Irannejad, Abbas Kebriaieezadeh, Afshin Zarghi, Farhad Montazer-Sadegh, Abbas Shafiee, Amir Assadieskandar, Mohsen Amini [Tehran University of Medical Sciences]

Bioorg. and Med.Chem., **22**, 865-873, 2014

A series of 5-Aryl-6-(4-methylsulfonyl)-3-(methylthio)-1,2,4-triazine derivatives were synthesized and their COX-1/COX-2 inhibitory activity as well as in vivo anti-inflammatory and analgesic effects were evaluated. All of compounds showed strong inhibition of COX-2 with IC₅₀ values in the range of 0.1–0.2 μ M and in most cases had stronger anti-inflammatory and analgesic effects than indomethacin at doses 3 and 6 mg/kg. Among them, 5-(4-chlorophenyl)-6-(4-(methylsulfonyl)phenyl)-3-(methylthio)-1,2,4-triazine (**9c**) was the most potent and selective COX-2 compound; its selectivity index of 395 was comparable to celecoxib (SI = 405).

Medicinal Chemistry and Drug Design (Cont'd)

Computational Modeling of an Epidermal Growth Factor Receptor Single-Mutation Resistance to Cetuximab in Colorectal Cancer Treatment

Ignasi Buch, Noelia Ferruz, Gianni De Fabritiis [Universitat Pompeu Fabra]

J.Chem. Infor. and Mod. **53**, 3123–3126, 2014.

Extracellular S468R mutation of the epidermal growth factor receptor (EGFR) was recently identified as the cause of resistance to cetuximab, a widely used drug in colorectal cancer treatment. Here, we have determined the binding free energies of cetuximab's Fab V_H - V_L domains and endogenous EGF ligand to wild type and S468R EGFR by high-throughput molecular dynamics. This work provides a possible mechanism of resistance in terms of increased competition, an hypothesis that can be further validated experimentally.

Antileishmanial phytochemical phenolics: Molecular docking to potential protein targets

Ifedayo Victor Ogungbe [Jackson State University], William R. Erwin, William N. Setzer

J. Mol.Graph. and Mod., **48**, 105-117, 2014.

A molecular docking analysis has been carried out to examine potential *Leishmania* protein targets of antiprotozoal plant-derived polyphenolic compounds. A total of 352 phenolic phytochemicals, including 10 auronones, six cannabinoids, 34 chalcones, 20 chromenes, 52 coumarins, 92 flavonoids, 41 isoflavonoids, 52 lignans, 25 quinones, eight stilbenoids, nine xanthonones, and three miscellaneous phenolic compounds, were used in the virtual screening study using 24 *Leishmania* enzymes (52 different protein structures from the Protein Data Bank).

Identification of p38 α MAP kinase inhibitors by pharmacophore based virtual screening

Rahul P. Gangwal, Nihar R. Das, Kaushik Thanki, Mangesh V. Damre, Gaurao V. Dhoke, Shyam S. Sharma, Sanyog Jain, Abhay T. Sangamwar [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Mol.Graph. and Mod., **49**, 18-24, 2014.

The p38 α mitogen-activated protein (MAP) kinase plays a vital role in treating many inflammatory diseases. In the present study, a combined ligand and structure based pharmacophore model was developed to identify potential DFG-in selective p38 MAP kinase inhibitors. Conformations of co-crystallised inhibitors were used in the development and validation of ligand and structure based pharmacophore modeling approached. The validated pharmacophore was utilized in database screening to identify potential hits. After Lipinski's rule of five filter and molecular docking analysis, nineteen hits were purchased and selected for *in vitro* analysis.

Discovery of potent inhibitor for matrix metalloproteinase-9 by pharmacophore based modeling and dynamics simulation studies

Sukesh Kalva, E.R. Azhagiya Singam, V. Rajapandian, Lilly M. Saleena [SRM University], V. Subramanian

J. Mol.Graph. and Mod., **49**, 25-37, 2014.

Matrix metalloproteinase-9 (MMP-9) is an attractive target for anticancer therapy. In the present study ligand based pharmacophore modeling was performed to elucidate the structural elements for a diverse class of MMP-9 inhibitors. The pharmacophore model was validated through Güner-Henry (GH) scoring method. The final pharmacophore model consisted of three hydrogen bond acceptors (HBA), and two ring aromatic regions (RA). This model was utilized to screen the natural compound database to seek novel compounds as MMP-9 inhibitors.

Medicinal Chemistry and Drug Design (Cont'd)

Prediction of Individual Compounds Forming Activity Cliffs Using Emerging Chemical Patterns

Vigneshwaran Namasivayam, Preeti Iyer, Jürgen Bajorath
[Rheinische Friedrich-Wilhelms-Universität Bonn]

J.Chem. Infor. and Mod. **53**, 3131–3139, 2014.

Activity cliffs are formed by structurally similar or analogous compounds having large potency differences. In medicinal chemistry, pairs or groups of compounds forming activity cliffs are of interest for structure–activity relationship (SAR) analysis and compound optimization. Thus far, activity cliff assessment has mostly been descriptive, i.e., compound data sets and activity landscape representations have been searched for activity cliffs in the context of SAR analysis. Only recently, first attempts have also been made to depart from descriptive analysis and predict activity cliffs.

Ligand- and Structure-Based Virtual Screening for Clathroдин-Derived Human Voltage-Gated Sodium Channel Modulators

Tihomir Tomašić, Basil Hartzoulakis, Nace Zidar, Fiona Chan, Robert W. Kirby, David J. Madge, Steve Peigneur, Jan Tytgat, Danijel Kikelj [University of Ljubljana]

J.Chem. Infor. and Mod. **53**, 3223–3232, 2014.

Voltage-gated sodium channels (VGSC) are attractive targets for drug discovery because of the broad therapeutic potential of their modulators. On the basis of the structure of marine alkaloid clathroдин, we have recently discovered novel subtype-selective VGSC modulators **I** and **II** that were used as starting points for two different ligand-based virtual screening approaches for discovery of novel VGSC modulators. Taken together, virtual screening yielded compounds **2** and **16**, which represent novel scaffolds for the discovery of human Na_v1.7 modulators.

A!

Economical and Accurate Protocol for Calculating Hydrogen-Bond-Acceptor Strengths

Ahmed El Kerdawy, Christofer S. Tautermann, Timothy Clark [Friedrich-Alexander-Universität Erlangen-Nürnberg], Thomas Fox

J.Chem. Infor. and Mod. **53**, 3262–3272, 2014.

A series of density functional/basis set combinations and second-order Møller–Plesset calculations have been used to test their ability to reproduce the trends observed experimentally for the strengths of hydrogen-bond acceptors in order to identify computationally efficient techniques for routine use in the computational drug-design process. The effects of functionals, basis sets, counterpoise corrections, and constraints on the optimized geometries were tested and analyzed, and recommendations (M06-2X/cc-pVDZ and X3LYP/cc-pVDZ with single-point counterpoise corrections or X3LYP/aug-cc-pVDZ without counterpoise) were made for suitable moderately high-throughput techniques.

De Novo Design of Drug-Like Molecules by a Fragment-Based Molecular Evolutionary Approach

Kentaro Kawai [Shinomiya Minamikawara-cho], Naoya Nagata, Yoshimasa Takahashi

J.Chem. Infor. and Mod. **54**, 49–56, 2014.

This paper describes a similarity-driven simple evolutionary approach to producing candidate molecules of new drugs. The aim of the method is to explore the candidates that are structurally similar to the reference molecule and yet somewhat different in not only peripheral chains but also their scaffolds. The method employs a known active molecule of our interest as a reference molecule which is used to navigate a huge chemical space. The reference molecule is also used to obtain seed fragments. An initial set of individual structures is prepared with the seed fragments and additional fragments using several connection rules.

Medicinal Chemistry and Drug Design (Cont'd)

Theoretical and Experimental Study of Inclusion Complexes Formed by Isoniazid and Modified β -Cyclodextrins: ^1H NMR Structural Determination and Antibacterial Activity Evaluation

Milena G. Teixeira, João V. de Assis, Cássia G. P. Soares, Mateus F. Venâncio, Juliana F. Lopes, Clebio S. Nascimento, Jr, Cleber P. A. Anconi, Guilherme S. L. Carvalho, Cristina S. Lourenço, Mauro V. de Almeida, Sergio A. Fernandes, Wagner B. de Almeida [Universidade Federal de Minas Gerais (UFMG)]

J. Phys. Chem. B., **118**, 81–93, 2014.

Me- β -cyclodextrin (Me- β CD) and HP- β -cyclodextrin (HP- β CD) inclusion complexes with isoniazid (INH) were prepared with the aim of modulating the physicochemical and biopharmaceutical properties of the guest molecule, a well-known antituberculosis drug. The architectures of the complexes were initially proposed according to NMR data Job plot and ROESY followed by density functional theory (DFT) calculations of ^1H NMR spectra using the PBE1PBE functional and 6-31G(d,p) basis set, including the water solvent effect with the polarizable continuum model (PCM), for various inclusion modes, providing support for the experimental proposal.

Drug Design Targeting Protein–Protein Interactions (PPIs) Using Multiple Ligand Simultaneous Docking (MLSD) and Drug Repositioning: Discovery of Raloxifene and Bazedoxifene as Novel Inhibitors of IL-6/GP130 Interface

Huameng Li, Hui Xiao, Li Lin, David Jou, Vandana Kumari, Jiayuh Lin, Chenglong Li [The Ohio State University]

J. Med. Chem., **57**, 632–641, 2014.

The IL-6/GP130/STAT3 pathway is critical for the progression of multiple types of cancers. We report here the discovery of raloxifene and bazedoxifene as novel inhibitors of IL-6/GP130 protein–protein interactions (PPIs) using multiple ligand simultaneous docking (MLSD) and drug repositioning approaches. Multiple drug scaffolds were simultaneously docked into hot spots of GP130 D1 domain by MLSD to compete with the key interacting residues of IL-6, followed by tethering to generate virtual hit compounds.

In Silico Design of Monomolecular Drug Carriers for the Tyrosine Kinase Inhibitor Drug Imatinib Based on Calix- and Thiacalix[n]arene Host Molecules: A DFT and Molecular Dynamics Study

Rodrigo Galindo-Murillo, María Eugenia Sandoval-Salinas, Joaquín Barroso-Flores [Centro Conjunto de Investigación en Química Sustentable UAEM-UNAM]

J. Chem. Theor. and Comp., **10**, 825–834, 2014.

The use of functionalized calix- and thia-calix[n]arenes is proposed as the basis for our *in silico* design of a suitable drug carrier for the tyrosine kinase inhibitor, Imatinib. Their mutual electronic properties and interaction energies, E_{int} , were assessed with the use of DFT methods under the NBODEl methodology. Three structural variables for the host molecules were considered: $R = \{\text{SO}_3\text{H}$ (1), $t\text{-Bu}$ (2), $i\text{-Pr}$ (3), COOH (4), $(\text{CH}_2)_2\text{OH}$ (5), $(\text{CH}_2)_2\text{NH}_2$ (6) $\}$; $b = \{\text{CH}_2, \text{S}\}$; $n = \{5, 6, 8\}$, and two possible orientations for the insertion of Imatinib within the macrocycle cavity: pyridine moiety pointing inward (N1) and piperazine pointing inward (N2).

Amphiphilic Drug-Like Molecules Accumulate in a Membrane below the Head Group Region

Markéta Paloncýová, Russell DeVane, Bruce Murch, Karel Berka, Michal Otyepka [Palacký University Olomouc]

J. Phys. Chem. B., **118**, 1030–1039, 2014.

The partitioning behavior of drug-like molecules into biomembranes has a crucial impact on the design and efficacy of therapeutic drugs. Thermodynamic properties connected with the interaction of molecules with membranes can be evaluated by calculating free-energy profiles normal to the membrane surface. We calculated the free-energy profiles of 25 drug-like molecules in a 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) membrane and free energies of solvation in water and heptane using two methods, molecular dynamics (MD) simulations with the Berger lipid force field and COSMOmic, based on a continuum conductor-like screening model for realistic solvation (COSMO-RS).

Quantitative Structure-Activity Relations

Multivariate SAR and QSAR of cucurbitacin derivatives as cytotoxic compounds in a human lung adenocarcinoma cell line

Karen L. Lang, Izabella T. Silva, Vanessa R. Machado, Lara A. Zimmermann, Miguel S.B. Caro, Cláudia M.O. Simões, Eloir P. Schenkel, Fernando J. Durán, Lílían S.C. Bernardes, Eduardo B. de Melo [Western Paraná State University (Unioeste)]

J. Mol. Graph. and Mod., **48**, 70-79, 2014.

The SAR study demonstrated that the presence or absence of cytotoxic activity of the cucurbitacins could be described using information derived from their chemical structures. The QSAR study displayed suitable internal and external predictivity, and the selected descriptors indicated that the observed activity might be related to electrophilic attack on cellular structures or genetic material. This study provides improves the understanding of the cytotoxic activity of cucurbitacins and could be used to propose new cytotoxic agents.

Combined QSAR and molecule docking studies on predicting P-glycoprotein inhibitors

Wen Tan, Hu Mei [Chongqing University], Li Chao, Tengfei Liu, Xianchao Pan, Mao Shu, i Yang

J. Comp. Aided. Mol. Design, **27**, 1067-1073, 2014.

Thus, designing effective P-gp inhibitors has an extremely important role in the overcoming MDR. In this paper, both ligand-based quantitative structure-activity relationship (QSAR) and receptor-based molecular docking are used to predict P-gp inhibitors. The results show that each method achieves good prediction performance. According to the results of tenfold cross-validation, an optimal linear SVM model with only three descriptors is established on 857 training samples, of which the overall accuracy (Acc), sensitivity, specificity, and Matthews correlation coefficient are 0.840, 0.873, 0.813, and 0.683, respectively.

Elaborate ligand-based modeling coupled with QSAR analysis and in silico screening reveal new potent acetylcholinesterase inhibitors

Sawsan Abuhamdah, Maha Habash, Mutasem O. Taha [The University of Jordan]

J. Comp. Aided. Mol. Design, **27**, 1075-1092, 2014.

Inhibition of the enzyme acetylcholinesterase (AChE) has been shown to alleviate neurodegenerative diseases prompting several attempts to discover and optimize new AChE inhibitors. In this direction, we explored the pharmacophoric space of 85 AChE inhibitors to identify high quality pharmacophores. Subsequently, we implemented genetic algorithm-based quantitative structure-activity relationship (QSAR) modeling to select optimal combination of pharmacophoric models and 2D physicochemical descriptors capable of explaining bioactivity variation among training compounds.

1.2. Biopolymers

Bioinformatics and Cheminformatics

myChEMBL: a virtual machine implementation of open data and cheminformatics tools

Rodrigo Ochoa, Mark Davies, George Papadatos, Francis Atkinson, John P. Overington [Wellcome Trust Genome Campus]

Bioinformatics. **30**, 298-300, 2014.

myChEMBL is a completely open platform, which combines public domain bioactivity data with open source database and cheminformatics technologies. myChEMBL consists of a Linux (Ubuntu) Virtual Machine featuring a PostgreSQL schema with the latest version of the ChEMBL database, as well as the latest RDKit cheminformatics libraries. In addition, a self-contained web interface is available, which can be modified and improved according to user specifications.

Bioinformatics and Cheminformatics (Cont'd)

Parallel implementation of 3D protein structure similarity searches using a GPU and the CUDA

Dariusz Mrozek[Silesian University of Technology], Miłosz Brożek, Bożena Małysiak-Mrozek

J. Mol.Mod., **20**, 20:2067, 2014.

Searching for similar 3D protein structures is one of the primary processes employed in the field of structural bioinformatics. However, the computational complexity of this process means that it is constantly necessary to search for new methods that can perform such a process faster and more efficiently. In this paper, we describe the GPU-based implementation of the CASSERT algorithm for 3D protein structure similarity searching. This algorithm is based on the two-phase alignment of protein structures when matching fragments of the compared proteins.

MDWiZ: A platform for the automated translation of molecular dynamics simulations

Victor H. Rusu, Vitor A.C. Horta, Bruno A.C. Horta, Roberto D. Lins, Riccardo Baron [The University of Utah]

J. Mol.Graph. and Mod., **48**, 80-86, 2014.

Here, we present the MDWiZ platform, a freely accessed online portal designed to aid the fast and reliable preparation and conversion of file formats that allows researchers to reproduce or generate data from MD simulations using different setups, including force fields and models with different underlying potential forms. The general structure of MDWiZ is presented, the features of version 1.0 are detailed, and an extensive validation based on GROMACS to LAMMPS conversion is presented. We believe that MDWiZ will be largely useful to the molecular dynamics community.

An Integrated Virtual Screening Approach for VEGFR-2 Inhibitors

Yanmin Zhang, Shangyan Yang, Yu Jiao, Haichun Liu, Haoliang Yuan, Shuai Lu, Ting Ran, Sihui Yao, Zhipeng Ke, Jinxing Xu, Xiao Xiong, Yadong Chen, Tao Lu [China Pharmaceutical University]

J.Chem. Infor. and Mod. **53**, 3163–3177, 2014.

A!

In recent years, various virtual screening (VS) tools have been developed, and many successful screening campaigns have been showcased. However, whether by conventional molecular docking or pharmacophore screening, the selection of virtual hits is based on the ranking of compounds by scoring functions or fit values, which remains the bottleneck of VS due to insufficient accuracy. As the limitations of individual methods persist, a comprehensive comparison and integration of different methods may provide insights into selecting suitable methods for VS. Here, we evaluated the performance of molecular docking, fingerprint-based 2D similarity and multicomplex pharmacophore in an individual and a combined manner, through a retrospective VS study on VEGFR-2 inhibitors.

Assessing Molecular Docking Tools for Relative Biological Activity Prediction: A Case Study of Triazole HIV-1 NNRTIs

Tomasz Frączek, Agata Siwek, Piotr Paneth [Lodz University of Technology]

J.Chem. Infor. and Mod. **53**, 3326–3342, 2014.

Molecular docking is a technique widely used in drug design. Many studies exist regarding the general accuracy of various docking programs, but case studies for a given group of related compounds are rare. In order to facilitate identification of novel triazole HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), several docking and scoring programs were evaluated for their ability to predict relative biological activity of 111 known 1,2,4-triazole and 76 other azole type NNRTIs. Glide, FlexX, Molegro Virtual Docker, AutoDock Vina, and Hyde were used.

Bioinformatics and Cheminformatics (Cont'd)

DR-Predictor: Incorporating Flexible Docking with Specialized Electronic Reactivity and Machine Learning Techniques to Predict CYP-Mediated Sites of Metabolism

Tao-wei Huang, Jed Zaretski, Charles Bergeron, Kristin P. Bennett, Curt M. Breneman [Rensselaer Polytechnic Institute]

J.Chem. Infor. and Mod. **53**, 3352–3366, 2014.

Computational methods that can identify CYP-mediated sites of metabolism (SOMs) of drug-like compounds have become required tools for early stage lead optimization. In recent years, methods that combine CYP binding site features with CYP/ligand binding information have been sought in order to increase the prediction accuracy of such hybrid models over those that use only one representation. We have created Docking-Regioselectivity-Predictor (DR-Predictor)—a method that incorporates flexible docking-derived information with specialized electronic reactivity and multiple-instance-learning methods to predict CYP-mediated SOMs.

SCISSORS: Practical Considerations

Steven M. Kearnes, Imran S. Haque, Vijay S. Pande [Stanford University]

J.Chem. Infor. and Mod. **54**, 5–15, 2014.

Molecular similarity has been effectively applied to many problems in cheminformatics and computational drug discovery, but modern methods can be prohibitively expensive for large-scale applications. The SCISSORS method rapidly approximates measures of pairwise molecular similarity such as ROCS and LINGO Tanimotos, acting as a filter to quickly reduce the size of a problem.

Prediction of New Bioactive Molecules using a Bayesian Belief Network

Ammar Abdo [Hodeidah University], Valérie Leclère, Philippe Jacques, Naomie Salim, Maude Pupin

J.Chem. Infor. and Mod. **54**, 30–36, 2014.

Natural products and synthetic compounds are a valuable source of new small molecules leading to novel drugs to cure diseases. However identifying new biologically active small molecules is still a challenge. In this paper, we introduce a new activity prediction approach using Bayesian belief network for classification (BBNC). The roots of the network are the fragments composing a compound. The leaves are, on one side, the activities to predict and, on another side, the unknown compound. The activities are represented by sets of known compounds, and sets of inactive compounds are also used.

MOSAIC: A Data Model and File Formats for Molecular Simulations

Konrad Hinsén [FranceSynchrotron SOLEIL]

J.Chem. Infor. and Mod. **54**, 131–137, 2014.

The MOlecular SimulAtion Interchange Conventions (MOSAIC) consist of a data model for molecular simulations and of concrete implementations of this data model in the form of file formats. MOSAIC is designed as a modular set of specifications, of which the initial version covers molecular structure and configurations. A reference implementation in the Python language facilitates the development of simulation software based on MOSAIC.

A!

Bioinformatics and Cheminformatics (Cont'd)

Fragment-based Shape Signatures: a new tool for virtual screening and drug discovery

Randy J. Zauhar [University of the Sciences, Philadelphia], Eleonora Gianti, William J. Welsh

J. Comp. Aided. Mol. Design, **27**, 1009-1036, 2014.

Since its introduction in 2003, the Shape Signatures method has been successfully applied in a number of drug design projects. Because it uses a ray-tracing approach to directly measure molecular shape and properties (as opposed to relying on chemical structure), it excels at scaffold hopping, and is extraordinarily easy to use. Despite its advantages, a significant drawback of the method has hampered its application to certain classes of problems; namely, when the chemical structures considered are large and contain heterogeneous ring-systems, the method produces descriptors that tend to merely measure the overall size of the molecule, and begin to lose selective power.

Protein models: The Grand Challenge of protein docking

Ivan Anishchenko, Petras J. Kundrotas, Alexander V. Tuzikov, Ilya A. Vakser [The University of Kansas]

Proteins: Stru. Fun. & Bioinf., **82**, 278–287, 2014.

Characterization of life processes at the molecular level requires structural details of protein–protein interactions (PPIs). The number of experimentally determined protein structures accounts only for a fraction of known proteins. This article presents such a suite of models built for the benchmark set of the X-ray structures from the DOCKGROUND resource (<http://dockground.bioinformatics.ku.edu>) by a combination of homology modeling and Nudged Elastic Band method.

Quantifying Artifacts in Ewald Simulations of Inhomogeneous Systems with a Net Charge

Jochen S. Hub, Bert L. de Groot, Helmut Grubmüller, Gerrit Groenhof [University of Jyväskylä]

J. Chem. Theor. and Comp, **10**, 381–390, 2014.

Ewald summation, which has become the *de facto* standard for computing electrostatic interactions in biomolecular simulations, formally requires that the simulation box is neutral. Here, we derive an analytical expression for the effect of using an implicit background charge instead of explicit counterions, on the chemical potential of ions in heterogeneous systems, which (i) provides a quantitative criterium for deciding if the background charge offers an acceptable trade-off between artifacts arising from sampling problems and artifacts arising from the homogeneous background charge distribution, and (ii) can be used to correct this artifact in certain cases.

Going Backward: A Flexible Geometric Approach to Reverse Transformation from Coarse Grained to Atomistic Models

Tsjerk A. Wassenaar [University of Calgary], Kristyna Pluhackova, Rainer A. Böckmann, Siewert J. Marrink, D. Peter Tieleman

J. Chem. Theor. and Comp, **10**, 676–690, 2014.

The conversion of coarse-grained to atomistic models is an important step in obtaining insight about atomistic scale processes from coarse-grained simulations. For this process, called backmapping or reverse transformation, several tools are available, but these commonly require libraries of molecule fragments or they are linked to a specific software package. Here, we present an alternative method, consisting of geometric projection and subsequent force-field based relaxation. This method is designed to be simple and flexible, and offers a generic solution for resolution transformation.

Comparative or Homology Modeling

Structural studies, homology modeling and molecular docking of novel non-competitive antagonists of GluK1/GluK2 receptors

Agnieszka A. Kaczor [University of Eastern Finland], Zbigniew Karczmarzyk, Andrzej Fruziński, Kalevi Pihlaja, Jari Sinkkonen, Kirsti Wiinämäki, Christiane Kronbach, Klaus Unverferth, Antti Poso, Dariusz Matosiuk

Bioorg. and Med.Chem., **22**, 787-795, 2014.

Non-competitive ligands of kainate receptors have focused significant attention as medicinal compounds because they seem to be better tolerated than competitive antagonists and uncompetitive blocker of these receptors. Here we present structural studies (X-ray structure determination, NMR and MS spectra) of novel indole-derived non-competitive antagonists of GluK1/GluK2 receptors, homology models of GluK1 and GluK2 receptors based on novel AMPA receptor template as well as molecular docking of ligands to their molecular targets.

Molecular Modeling of the 3D Structure of 5-HT_{1A}R: Discovery of Novel 5-HT_{1A}R Agonists via Dynamic Pharmacophore-Based Virtual Screening

Lili Xu, Shanglin Zhou, Kunqian Yu, Bo Gao, Hualiang Jiang, Xuechu Zhen, Wei Fu [Fudan University]

J.Chem. Infor. and Mod. **53**, 3202–3211, 2014.

A!

The serotonin receptor subtype 1A (5-HT_{1A}R) has been implicated in several neurological conditions, and potent 5-HT_{1A}R agonists have therapeutic potential for the treatment of depression, anxiety, schizophrenia, and Parkinson's disease. In the present study, a homology model of 5-HT_{1A}R was built based on the latest released high-resolution crystal structure of the β_2 AR in its active state (PDB: 3SN6). A dynamic pharmacophore model, which takes the receptor flexibility into account, was constructed, validated, and applied to our dynamic pharmacophore-based virtual screening approach with the aim to identify potential 5-HT_{1A}R agonists.

Homology Modeling of Human Muscarinic Acetylcholine Receptors

Trayder Thomas, Kimberley C. McLean, Fiona M. McRobb, David T. Manallack, David K. Chalmers, Elizabeth Yuriev [Monash University (Parkville Campus)]

J.Chem. Infor. and Mod. **54**, 243–253, 2014.

We have developed homology models of the acetylcholine muscarinic receptors M₁R–M₅R, based on the β_2 -adrenergic receptor crystal as the template. This is the first report of homology modeling of all five subtypes of acetylcholine muscarinic receptors with binding sites optimized for ligand binding. The models were evaluated for their ability to discriminate between muscarinic antagonists and decoy compounds using virtual screening using enrichment factors, area under the ROC curve (AUC), and an early enrichment measure, LogAUC. The models produce rational binding modes of docked ligands as well as good enrichment capacity when tested against property-matched decoy libraries, which demonstrates their unbiased predictive ability.

Free Energy Simulations of Binding of HsTx1 Toxin to Kv1 Potassium Channels: the Basis of Kv1.3/Kv1.1 Selectivity

M. Harunur Rashid , Serdar Kuyucak [University of Sydney]

J. Phys. Chem. B., **118**, 707–716, 2014.

A!

The voltage-gated potassium channel Kv1.3 is an established target for treatment of autoimmune diseases. Hence, there are intense efforts to develop immunosuppressant drugs from Kv1.3 blockers. ShK toxin from sea anemone is the most advanced peptide in this regard, but its lack of selectivity for Kv1.3 over Kv1.1 is an ongoing concern. Here we construct accurate models of Kv1.x–HsTx1 complexes using docking and MD simulations. For each complex, the binding free energy of HsTx1 is determined from the potential of mean force calculations.

Protein Conformational Analysis

Ligand Concentration Regulates the Pathways of Coupled Protein Folding and Binding

Kyle G. Daniels, Nam K. Tonthat, David R. McClure, Yu-Chu Chang, Xin Liu, Maria A. Schumacher, Carol A. Fierke, Scott C. Schmidler, and Terrence G. Oas [Duke University Medical Center]

J. Am. Chem. Soc., **136**, 822–825, 2014.

Coupled ligand binding and conformational change plays a central role in biological regulation. Ligands often regulate protein function by modulating conformational dynamics, yet the order in which binding and conformational change occurs are often hotly debated. Here we show that the “conformational selection versus induced fit” distinction on which this debate is based is a false dichotomy because the mechanism depends on ligand concentration. Using the binding of pyrophosphate (PPi) to *Bacillus subtilis* RNase P protein as a model, we show that coupled reactions are best understood as a change in flux between competing pathways with distinct orders of binding and conformational change.

Insights on the Facet Specific Adsorption of Amino Acids and Peptides toward Platinum

Sathish Kumar Ramakrishnan, Marta Martin, Thierry Cloitre, Lucyna Firlej, Frédéric J. G. Cuisinier, Csilla Gergely [Université Montpellier 2]

J. Chem. Infor. and Mod. **53**, 3273–3279, 2014.

Engineering shape-controlled bionanomaterials requires comprehensive understanding of interactions between biomolecules and inorganic surfaces. We explore the origin of facet-selective binding of peptides adsorbed onto Pt(100) and Pt(111) crystallographic planes. Using molecular dynamics simulations, we show that upon adsorption the peptides adopt a predictable conformation. We compute the binding energies of the amino acids constituting two adhesion peptides for Pt, S7, and T7 and demonstrate that peptides’ surface recognition behavior that makes them unique among populations originates from differential adsorption of their building blocks.

A!

Exploiting Conformational Dynamics in Drug Discovery: Design of C-Terminal Inhibitors of Hsp90 with Improved Activities

Elisabetta Moroni, Huiping Zhao, Brian S. J. Blagg, Giorgio Colombo [Istituto di chimica del riconoscimento molecolare]

J. Chem. Infor. and Mod. **54**, 195–208, 2014.

The interaction that occurs between molecules is a dynamic process that impacts both structural and conformational properties of the ligand and the ligand binding site. Herein, we investigate the dynamic cross-talk between a protein and the ligand as a source for new opportunities in ligand design. Analysis of the formation/disappearance of protein pockets produced in response to a first-generation inhibitor assisted in the identification of functional groups that could be introduced onto scaffolds to facilitate optimal binding, which allowed for increased binding with previously uncharacterized regions.

DockRank: Ranking docked conformations using partner-specific sequence homology-based protein interface prediction

Li C. Xue, Rafael A. Jordan, EL-Manzalawy Yasser, Drena Dobbs, Vasant Honavar [Iowa State University]

Proteins: Stru. Fun. & Bioinf., **82**, 250–267, 2014.

Selecting near-native conformations from the immense number of conformations generated by docking programs remains a major challenge in molecular docking. We introduce DockRank, a novel approach to scoring docked conformations based on the degree to which the interface residues of the docked conformation match a set of predicted interface residues. DockRank uses interface residues predicted by partner-specific sequence homology-based protein–protein interface predictor (PS-HomPPI), which predicts the interface residues of a query protein with a specific interaction partner.

Protein Conformational Analysis (Cont'd)

Molecular dynamics simulations reveal that apo-HisJ can sample a closed conformation

B. C. H. Chu, D. I. Chan, T. DeWolf, X. Periole, H. J. Vogel
[University of Calgary]

Proteins: Stru. Fun. & Bioinf., **82**, 386–398, 2014.

A!

The *Escherichia coli* histidine binding protein HisJ is a type II periplasmic binding protein (PBP) that preferentially binds histidine and interacts with its cytoplasmic membrane ABC transporter, HisQMP₂, to initiate histidine transport. To explore the accessibility of the closed conformation to the apo state of the protein, we performed a set of all-atom molecular dynamics simulations of HisJ starting from four different conformations: apo-open, apo-closed, apo-semiopen, and holo-closed.

Applying conformational selection theory to improve crossdocking efficiency in 3-phosphoinositide dependent protein kinase-1

Anuja Kotasthane, Chandrika Mulakala [Jubilant Biosys Limited] Vellarkad N. Viswanadhan

Proteins: Stru. Fun. & Bioinf., **82**, 436–451, 2014.

The emerging picture of biomolecular recognition is that of conformational selection followed by induced-fit. Conformational selection theory states that binding partners exist in various conformations in solution, with binding involving a “selection” between complementary conformers. In this study, we devise a docking protocol that mimics conformational selection in protein–ligand binding and demonstrate that it significantly enhances crossdocking accuracy over Glide's flexible docking protocol, which is widely used in the pharmaceutical industry.

Exploring Transition Pathway and Free-Energy Profile of Large-Scale Protein Conformational Change by Combining Normal Mode Analysis and Umbrella Sampling Molecular Dynamics

Jinan Wang, Qiang Shao, Zhijian Xu, Yingtao Liu, Zhuo Yang, Benjamin P. Cossins, Hualiang Jiang, Kaixian Chen, Jiye Shi, and Weiliang Zhu [Chinese Academy of Sciences]

J. Phys. Chem. B., **118**, 134–143, 2014.

Large-scale conformational changes of proteins are usually associated with the binding of ligands. Because the conformational changes are often related to the biological functions of proteins, understanding the molecular mechanisms of these motions and the effects of ligand binding becomes very necessary. In the present study, we use the combination of normal-mode analysis and umbrella sampling MD simulation to delineate the atomically detailed conformational transition pathways and the associated free-energy landscapes for three well-known protein systems, in the absence and presence of respective ligands.

Protein Structure Analysis

mulPBA: an efficient multiple protein structure alignment method based on a structural alphabet

Sylvain Léonard, Agnel Praveen Joseph, Narayanaswamy Srinivasan, Jean-Christophe Gelly & Alexandre G. de Brevern [Univ Paris Diderot]

J. Biomol. Stru. and Dyn., **32**, 661–668, 2014.

The increasing number of available protein structures requires efficient tools for multiple structure comparison. Indeed, multiple structural alignments are essential for the analysis of function, evolution and architecture of protein structures. For this purpose, we proposed a new web server called multiple Protein Block Alignment. This server implements a method based on a structural alphabet to describe the backbone conformation of a protein chain in terms of dihedral angles. This ‘sequence-like’ representation enables the use of powerful sequence alignment methods for primary structure comparison.

Protein Structure Analysis (Cont'd)

Quantitative characterization of protein tertiary motifs

Rajani R. Joshi [IIT Bombay], S. Sreenath

J. Mol.Mod., **20**, 20:2077, 2014.

A quantitative feature-vector representation/model of tertiary structural motifs of proteins is presented. Multiclass logistic regression and a probabilistic neural network were employed to apply this representation to large data sets in order to classify them into major families of distinct motif types (including those of functional importance) with high statistical confidence. Scatter plots of random samples of these motifs were obtained through two-dimensional transformation of the feature vector by metric MDS (multidimensional scaling).

Modules Identification in Protein Structures: The Topological and Geometrical Solutions

Setareh Tasdighian, Luisa Di Paola [Università CAMPUS BioMedico], Micol De Ruvo, Paola Paci, Daniele Santoni, Pasquale Palumbo, Giampiero Mei, Almerinda Di Venere, Alessandro Giuliani

J.Chem. Infor. and Mod. **54**, 159–168, 2014.

The identification of modules in protein structures has major relevance in structural biology, with consequences in protein stability and functional classification, adding new perspectives in drug design. In this work, we present the comparison between a topological (spectral clustering) and a geometrical (*k*-means) approach to module identification, in the frame of a multiscale analysis of the protein architecture principles. The peculiar “small-world” character of protein contact graphs is established as well, pointing to average shortest path as a mesoscopic crucial variable to maximize the efficiency of within-molecule signal transmission.

Dihedral-Based Segment Identification and Classification of Biopolymers I: Proteins

Gabor Nagy, Chris Oostenbrink [University of Natural Resources and Life Sciences, Muthgasse 18]

J.Chem. Infor. and Mod. **54**, 266–277, 2014.

A new structure classification scheme for biopolymers is introduced, which is solely based on main-chain dihedral angles. It is shown that by dividing a biopolymer into segments containing two central residues, a local classification can be performed. The method is referred to as DISICL, short for Dihedral-based Segment Identification and Classification. Compared to other popular secondary structure classification programs, DISICL is more detailed as it offers 18 distinct structural classes, which may be simplified into a classification in terms of seven more general classes.

Dihedral-Based Segment Identification and Classification of Biopolymers II: Polynucleotides

Gabor Nagy, Chris Oostenbrink [University of Natural Resources and Life Sciences, Muthgasse 18]

J.Chem. Infor. and Mod. **54**, 278–288, 2014.

In an accompanying paper (Nagy, G.; Oostenbrink, C. Dihedral-based segment identification and classification of biopolymers I: Proteins. *J. Chem. Inf. Model.* 2013, DOI: 10.1021/ci400541d), we introduce a new algorithm for structure classification of biopolymeric structures based on main-chain dihedral angles. The DISICL algorithm (short for Dihedral-based Segment Identification and Classification) classifies segments of structures containing two central residues. Here, we introduce the DISICL library for polynucleotides, which is based on the dihedral angles ε , ζ , and χ for the two central residues of a three-nucleotide segment of a single strand.

Protein Structure Analysis (Cont'd)

Formulation of probabilistic models of protein structure in atomic detail using the reference ratio method

Jan B. Valentin, Christian Andreetta, Wouter Boomsma, Sandro Bottaro, Jesper Ferkinghoff-Borg, Jes Frellsen, Kanti V. Mardia, Pengfei Tian, Thomas Hamelryck [University of Copenhagen]

Proteins: Stru. Fun. & Bioinf., **82**, 288–299, 2014.

We propose a method to formulate probabilistic models of protein structure in atomic detail, for a given amino acid sequence, based on Bayesian principles, while retaining a close link to physics. We start from two previously developed probabilistic models of protein structure on a local length scale, which concern the dihedral angles in main chain and side chains, respectively. Conceptually, this constitutes a probabilistic and continuous alternative to the use of discrete fragment and rotamer libraries.

Sensitivity of ab Initio vs Empirical Methods in Computing Structural Effects on NMR Chemical Shifts for the Example of Peptides

Chris Vanessa Sumowski, Matti Hanni, Sabine Schweizer, Christian Ochsenfeld [University of Munich (LMU)]

J. Chem. Theor. and Comp., **10**, 122–133, 2014.

The structural sensitivity of NMR chemical shifts as computed by quantum chemical methods is compared to a variety of empirical approaches for the example of a prototypical peptide, the 38-residue kalitoxin KTX comprising 573 atoms. Despite the simplicity of empirical chemical shift prediction programs, the agreement with experimental results is rather good, underlining their usefulness. However, we show in our present work that they are highly insensitive to structural changes, which renders their use for validating predicted structures questionable.

The gp41_{659–671} HIV-1 Antibody Epitope: A Structurally Challenging Small Peptide

Yuan Zhang, Celeste Sagui [North Carolina State University]

J. Phys. Chem. B., **118**, 69–80, 2014.

We report on extensive molecular dynamics (MD) simulations of the tridecapeptide corresponding to residues 659–671 of the envelope glycoprotein gp41 of HIV-1, which spans the 2F5 monoclonal antibody epitope ELDKWA. Previously, X-ray crystallography, nuclear magnetic resonance, and circular dichroism experiments have yielded conflicting conformational information, but there is a growing consensus that the monomeric peptide in aqueous solution is disordered. Here, we use the latest, state-of-the-art AMBER force fields to describe the complex conformational landscape of gp41_{659–671}.

A!

Protein Dynamics

Molecular dynamics studies on both bound and unbound renin protease

Natércia F. Brás, Pedro A. Fernandes, Maria J. Ramos [Universidade do Porto]

J. Biomol. Stru. and Dyn., **32**, 351–363, 2014.

The aspartic protease renin (REN) catalyses the rate-limiting step in the Renin–Angiotensin–Aldosterone System (RAAS), which regulates cardiovascular and renal homeostasis in living organisms. Renin blockage is therefore an attractive therapeutic strategy for the treatment of hypertension. Herein, computational approaches were used to provide a structural characterization of the binding site, flap opening and dynamic rearrangements of REN in the key conserved residues and water molecules, with the binding of a dodecapeptide substrate or different inhibitors.

Protein Dynamics (Cont'd)

Protein dynamics and motions in relation to their functions: several case studies and the underlying mechanisms

Li-Quan Yang, Peng Sang, Yan Tao, Yun-Xin Fu, Ke-Qin Zhang, Yue-Hui Xie, Shu-Qun Liu [Yunnan University]

J. Biomol. Stru. and Dyn., **32**, 372-393, 2014.

Proteins are dynamic entities in cellular solution with functions governed essentially by their dynamic personalities. We review several dynamics studies on serine protease proteinase K and HIV-1 gp120 envelope glycoprotein to demonstrate the importance of investigating the dynamic behaviors and molecular motions for a complete understanding of their structure–function relationships. Using computer simulations and essential dynamic (ED) analysis approaches, the dynamics data obtained revealed.

Effect of glycerol–water binary mixtures on the structure and dynamics of protein solutions

Pavan K. GhattyVenkataKrishna [Oak Ridge National Laboratory], Gustavo A. Carri

J. Biomol. Stru. and Dyn., **32**, 424-437, 2014.

We have performed 20 ns of fully atomistic molecular dynamics simulations of Hen Egg-White Lysozyme in 0, 10, 20, 30, and 100% by weight of glycerol in water to better understand the microscopic physics behind the bioprotection offered by glycerol to naturally occurring biological systems. The solvent exposure of protein surface residues changes when glycerol is introduced. The dynamic behavior of the protein, as quantified by the incoherent intermediate scattering function, shows a nonmonotonic dependence on glycerol content. The fluctuations of the protein residues with respect to each other were found to be similar in all water-containing solvents, but different from the pure glycerol case.

Motional timescale predictions by molecular dynamics simulations: Case study using proline and hydroxyproline sidechain dynamics

Abil E. Aliev [University College London], Martin Kulke, Harmeet S. Khaneja, Vijay Chudasama, Tom D. Sheppard and Rachel M. Lanigan

Proteins: Stru. Fun. & Bioinf., **82**, 195–215, 2014.

We propose a new approach for force field optimizations which aims at reproducing dynamics characteristics using biomolecular MD simulations, in addition to improved prediction of motionally averaged structural properties available from experiment. As the source of experimental data for dynamics fittings, we use ^{13}C NMR spin-lattice relaxation times T_1 of backbone and sidechain carbons, which allow to determine correlation times of both overall molecular and intramolecular motions.

Wild type and mutants of the HET-s(218–289) prion show different flexibility at fibrillar ends: A simulation study

Ran Friedman, Amedeo Caflisch [University of Zürich]

Proteins: Stru. Fun. & Bioinf., **82**, 399–404, 2014.

The C-terminal segment (residues 218–289) of the HET-s protein of the filamentous fungus *Podosporina anserina* is a prion-forming domain. The structural model of the HET-s(218–289) amyloid fibril based on solid-state nuclear magnetic resonance (NMR) restraints shows a β solenoid topology which is comprised of a β -sheet core and interconnecting loops. Here we have used molecular dynamics to compare the flexibility of the mutants and wild type.

Protein Dynamics (Cont'd)

Evaluation of Proteins' Rotational Diffusion Coefficients from Simulations of Their Free Brownian Motion in Volume-Occupied Environments

Maciej Długosz [University of Warsaw] , Jan M. Antosiewicz

J. Chem. Theor. and Comp, **10**, 481–491, 2014.

We have investigated the rotational dynamics of hen egg white lysozyme in monodisperse aqueous solutions of concentrations up to 250 mg/mL, using a rigid-body Brownian dynamics method that accurately accounts for anisotropies of diffusing objects. We have examined the validity of the free diffusion concept in the analysis of computer simulations of volume-occupied molecular solutions. We have found that, when as the only intermolecular interaction, the excluded volume effect is considered, rotational diffusion of molecules adheres to the free diffusion model.

Sampling the Denatured State of Polypeptides in Water, Urea, and Guanidine Chloride to Strict Equilibrium Conditions with the Help of Massively Parallel Computers

Roberto Meloni, Carlo Camilloni, Guido Tiana [Università degli Studi di Milano]

J. Chem. Theor. and Comp, **10**, 846–854, 2014.

The denatured state of polypeptides and proteins, stabilized by chemical denaturants like urea and guanidine chloride, displays residual secondary structure when studied by nuclear-magnetic-resonance spectroscopy. However, these experimental techniques are weakly sensitive, and thus molecular-dynamics simulations can be useful to complement the experimental findings. To sample the denatured state, we made use of massively-parallel computers and of a variant of the replica exchange algorithm, in which the different branches, connected with unbiased replicas, favor the formation and disruption of local secondary structure.

Amide-I Characteristics of Helical β -Peptides by Linear Infrared Measurement and Computations

Juan Zhao, Jipei Shi, Jianping Wang [Chinese Academy of Sciences]

J. Phys. Chem. B., **118**, 94–106, 2014.

In this work, we have examined the amide-I characteristics of three β -peptide oligomers in typical helical conformations (two in 14-helix and one in 12/10-helix), solvated in water, methanol, and chloroform, respectively. Local-mode frequencies and their distributions were computed using a molecular-mechanics force field based frequency map that was constructed on the basis of molecular dynamics simulations. The local-mode frequencies were found to be determined primarily by peptide backbone and side chain, rather by solvent, suggesting their local structural sensitivities.

Electrostatic Unfolding and Interactions of Albumin Driven by pH Changes: A Molecular Dynamics Study

K. Baler, O. A. Martin, M. A. Carignano, G. A. Ameer, J. A. Vila, I. Szleifer [Northwestern University]

J. Phys. Chem. B., **118**, 921–930, 2014.

A better understanding of protein aggregation is bound to translate into critical advances in several areas, including the treatment of misfolded protein disorders and the development of self-assembling biomaterials for novel commercial applications. Because of its ubiquity and clinical potential, albumin is one of the best-characterized models in protein aggregation research; but its properties in different conditions are not completely understood. Here, we carried out all-atom MD simulations of albumin to understand how electrostatics can affect the conformation of a single albumin molecule just prior to self-assembly.

Protein Dynamics (Cont'd)

A Kinetic Approach to the Sequence–Aggregation Relationship in Disease-Related Protein Assembly

Bogdan Barz, David J. Wales, Birgit Strodel [Heinrich Heine University Düsseldorf]

J. Phys. Chem. B., **118**, 1003–1011, 2014.

It is generally accepted that oligomers of aggregating proteins play an important role in the onset of neurodegenerative diseases. While *in silico* aggregation studies of full length amyloidogenic proteins are computationally expensive, the assembly of short protein fragments derived from these proteins with similar aggregating properties has been extensively studied. In the present work, MD simulations are performed to follow peptide aggregation on the microsecond time scale. By defining aggregation states, we identify transition networks, disconnectivity graphs, and first passage time distributions to describe the kinetics of the assembly process.

Free Energy Calculations

Accuracy Assessment and Automation of Free Energy Calculations for Drug Design

Clara D. Christ, Thomas Fox [Boehringer Ingelheim Pharma GmbH & Co. KG]

J. Chem. Infor. and Mod. **54**, 108–120, 2014.

As the free energy of binding of a ligand to its target is one of the crucial optimization parameters in drug design, its accurate prediction is highly desirable. In the present study we have assessed the average accuracy of free energy calculations for a total of 92 ligands binding to five different targets. To make this study and future larger scale applications possible we automated the setup procedure. Starting from user defined binding modes, the procedure decides which ligands to connect via a perturbation based on maximum common substructure criteria and produces all necessary parameter files for free energy calculations in AMBER 11.

Monte Carlo Free Ligand Diffusion with Markov State Model Analysis and Absolute Binding Free Energy Calculations

Ryoji Takahashi, Víctor A. Gil, Victor Guallar [Institutió Catalana de Recerca i Estudis Avançats (ICREA)]

J. Chem. Theor. and Comp., **10**, 282–288, 2014.

Obtaining absolute binding free energies from unbiased ligand diffusion has attracted a significant amount of attention due to its implications in drug design. Several studies have used special purpose computers and software to achieve microsecond molecular dynamics which, combined with a Markov state model analysis, are capable of providing absolute binding free energies. We demonstrate here the capabilities of our Monte Carlo technique in obtaining absolute binding free energies for a series of benzamidine like inhibitors into trypsin.

Adaptive Biasing Combined with Hamiltonian Replica Exchange to Improve Umbrella Sampling Free Energy Simulations

Fabian Zeller, Martin Zacharias [Technische Universität München]

J. Chem. Theor. and Comp., **10**, 703–710, 2014.

The accurate calculation of potentials of mean force for ligand–receptor binding is one of the most important applications of molecular simulation techniques. Typically, the separation distance between ligand and receptor is chosen as a reaction coordinate along which a PMF can be calculated with the aid of umbrella sampling (US) techniques. An approach combining such phase space reduction with flattening of the free energy landscape and configurational exchanges has been developed.

Ligand Binding/Docking

Comparative molecular field analysis of fenoterol derivatives interacting with an agonist-stabilized form of the β_2 -adrenergic receptor

Anita Plazinska, Karolina Pajak, Ewelina Rutkowska, Lucita Jimenez, Joseph Kozocas, Gary Koolpe, Mary Tanga, Lawrence Toll, Irving W. Wainer, Krzysztof Jozwiak [Medical University of Lublin]

Bioorg. and Med.Chem., **22**, 234-246, 2014.

The β_2 -adrenergic receptor (β_2 -AR) agonist [^3H]-(*R,R'*)-methoxyfenoterol was employed as the marker ligand in displacement studies measuring the binding affinities (K_i values) of the stereoisomers of a series of 4'-methoxyfenoterol analogs in which the length of the alkyl substituent at α' position was varied from 0 to 3 carbon atoms. The binding affinities of the compounds were additionally determined using the inverse agonist [^3H]-CGP-12177 as the marker ligand and the ability of the compounds to stimulate cAMP accumulation, measured as EC_{50} values, were determined in HEK293 cells expressing the β_2 -AR. The data indicate that the highest binding affinities and functional activities were produced by methyl and ethyl substituents at the α' position.

Predicting GPCR Promiscuity Using Binding Site Features

Anat Levit, Thijs Beuming, Goran Krilov, Woody Sherman, Masha Y. Niv [The Hebrew University]

J.Chem. Infor. and Mod. **54**, 184–194, 2014.

G protein-coupled receptors (GPCRs) represent a large family of signaling proteins that includes many therapeutic targets. GPCR ligands include odorants, tastants, and neurotransmitters and vary in size and properties. We perform statistical analysis using more than 30 descriptors related to the sequence, physicochemical, structural, and energetic properties of the GPCR binding sites—we find that the chemical variability of antagonists significantly correlates with the binding site hydrophobicity and anticorrelates with the number of hydrogen bond donors in the binding site.

Molecular dynamic simulations reveal the mechanism of binding between xanthine inhibitors and DPP-4

Yongliang Gu, Wei Wang, Xiaolei Zhu [Nanjing University of Technology], Keke Dong

J. Mol.Mod., **20**, 20:2075, 2014.

We apply molecular docking, molecular dynamics (MD) simulation, and binding free energy calculation to investigate and reveal the binding mechanism between five xanthine inhibitors and DPP-4. The electrostatic and van der Waals interactions of the five inhibitors with DPP-4 are analyzed and discussed. The computed binding free energies using MM-PBSA method are in qualitative agreement with experimental inhibitory potency of five inhibitors.

Exploration of the binding mode between (–)-zampanolide and tubulin using docking and molecular dynamics simulation

Si-Yan Liao, Guang-Quan Mo [Guangzhou Medical University], Jin-Can Chen, Kang-Cheng Zheng

J. Mol.Mod., **20**, 20:2070, 2014.

The study revealed that hydrophobic interactions play an important role in stabilizing the binding, and the strong hydrogen bond formed with Asp224 enhances the affinity for tubulin. Meanwhile, the results support the assumption that (–)-ZMP can be attacked by His227, leading to a nucleophilic reaction and covalent binding. These theoretical results lead to a greater understanding of the mechanism of action of binding to tubulin, and will therefore aid the design of new compounds with higher affinities for tubulin.

Ligand Binding / Docking (Cont'd)

Insight into the structural mechanism for PKB α allosteric inhibition by molecular dynamics simulations and free energy calculations

Shi-Feng Chen, Yang Cao, Shuang Han, Jian-Zhong Chen
[Zhejiang University]

J. Mol. Graph. and Mod., **48**, 36-46, 2014.

Protein kinase B (PKB/Akt) is an attractive target for the treatment of tumor. In the present studies, MD simulations were performed on three allosteric inhibitors with different inhibitory potencies (IC_{50}) to investigate the interaction modes between the inhibitors and PKB α . MM/GB(PB)SA were further applied to calculate the binding free energies of these inhibitors binding to PKB α . The computed binding free energies were consistent with the ranking of their experimental bioactivities.

Comparative Study on the Use of Docking and Bayesian Categorization To Predict Ligand Binding to Nicotinic Acetylcholine Receptors (nAChRs) Subtypes

David C. Kombo, Merouane Bencherif

J. Chem. Infor. and Mod. **53**, 3212–3222, 2014.

We have carried out a comparative study between docking into homology models and Bayesian categorization, as applied to virtual screening of nicotinic ligands for binding at various nAChRs subtypes (human and rat $\alpha 4\beta 2$, $\alpha 7$, $\alpha 3\beta 4$, and $\alpha 6\beta 2\beta 3$). We found that although results vary with receptor subtype, Bayesian categorization exhibits higher accuracy and enrichment than unconstrained docking into homology models. However, docking accuracy is improved when one sets up a hydrogen-bond (HB) constraint between the cationic center of the ligand and the main-chain carbonyl group of the conserved Trp-149 or its homologue (a residue involved in cation- π interactions with the ligand basic nitrogen atom).

Entropic and Enthalpic Contributions to Stereospecific Ligand Binding from Enhanced Sampling Methods

Balder Lai, Gabor Nagy, Jose Antonio Garate, Chris Oostenbrink [University of Natural Resources and Life Sciences, Muthgasse 18]

J. Chem. Infor. and Mod. **54**, 151–158, 2014.

The stereoselective binding of R- and S-propranolol to the metabolic enzyme cytochrome P450 2D6 and its mutant F483A was studied using various computational approaches. Previously reported free-energy differences from Hamiltonian replica exchange simulations, combined with thermodynamic integration, are compared to the one-step perturbation approach, combined with local-elevation enhanced sampling, and an excellent agreement between methods was obtained.

Identifying ligand binding sites and poses using GPU-accelerated Hamiltonian replica exchange molecular dynamics

Kai Wang, John D. Chodera, Yanzhi Yang, Michael R. Shirts
[University of Virginia]

J. Comp. Aided. Mol. Design, **27**, 989-1007, 2014.

We present a method to identify small molecule ligand binding sites and poses within a given protein crystal structure using GPU-accelerated Hamiltonian replica exchange molecular dynamics simulations. The Hamiltonians used vary from the physical end state of protein interacting with the ligand to an unphysical end state where the ligand does not interact with the protein. As replicas explore the space of Hamiltonians interpolating between these states, the ligand can rapidly escape local minima and explore potential binding sites.

Ligand Binding / Docking (Cont'd)

Simultaneous prediction of binding free energy and specificity for PDZ domain–peptide interactions

Joseph J. Crivelli, Gordon Lemmon, Kristian W. Kaufmann, Jens Meiler [Vanderbilt University]

J. Comp. Aided. Mol. Design, **27**, 1051-1065, 2014.

Interactions between protein domains and linear peptides underlie many biological processes. Among these interactions, the recognition of C-terminal peptides by PDZ domains is one of the most ubiquitous. In this work, we present a mathematical model for PDZ domain–peptide interactions capable of predicting both affinity and specificity of binding based on X-ray crystal structures and comparative modeling with ROSETTA. We developed our mathematical model using a large phage display dataset describing binding specificity for a wild type PDZ domain and 91 single mutants, as well as binding affinity data for a wild type PDZ domain binding to 28 different peptides.

Enzyme Catalysis

Comparative molecular dynamic simulations of wild type and Thr114Val mutated *Scaptodrosophila lebanonensis* alcohol dehydrogenase

Yimingjiang Wuxiuer, Jan-Olof Winberg, Ingebrigt Sylte [University of Tromsø]

J. Biomol. Stru. and Dyn., **32**, 465-476, 2014.

Enzyme kinetics studies have shown that *Scaptodrosophila lebanonensis* alcohol dehydrogenase (SIADH) and other drosophilid alcohol dehydrogenases function by a compulsory-ordered mechanism where the coenzyme binds to the free enzyme, and that a proton is released upon formation of the binary enzyme-NAD⁺ complex. A proton relay mechanism for the proton abstraction has been suggested that includes an eight-membered chain of water molecules connecting the active site with the bulk solvent. In the present study, comparative MD simulations of the wild type and the SIADH^{T114V} were performed.

Discovery of novel urokinase plasminogen activator (uPA) inhibitors using ligand-based modeling and virtual screening followed by in vitro analysis

Mahmoud A. Al-Sha'er, Mohammad A. Khanfar, Mutasem O. Taha [University of Jordan]

J. Mol.Mod., **20**, 20:2080, 2014.

Urokinase plasminogen activator (uPA)—a serine protease—is thought to play a central role in tumor metastasis and angiogenesis and, therefore, inhibition of this enzyme could be beneficial in treating cancer. We employed genetic algorithm-based quantitative structure-activity relationship (QSAR) analysis as a competition arena to select the best possible combination of pharmacophoric models and physicochemical descriptors that can explain bioactivity variation within the training inhibitors ($r^2_{162} = 0.74$, F-statistic = 64.30, $r^2_{LOO} = 0.71$, r^2_{PRESS} against 40 test inhibitors = 0.79).

Unconventional Plasticity of HIV-1 Reverse Transcriptase: How Inhibitors Could Open a Connection “Gate” between Allosteric and Catalytic Sites

Luca Bellucci, Lucilla Angeli, Andrea Tafi, Marco Radi, Maurizio Botta [Università degli Studi di Siena]

J.Chem. Infor. and Mod. **53**, 3117-3122, 2014.

Targeted molecular dynamics (TMD) simulations allowed for identifying the chemical/structural features of the nucleotide-competitive HIV-1 inhibitor DAVP-1, which is responsible for the disruption of the T-shape motif between Try183 and Trp229 of the reverse transcriptase (RT). DAVP-1 promoted the opening of a connection “gate” between allosteric and catalytic sites of HIV-1 RT, thus explaining its peculiar mechanism of action and providing useful insights to develop novel nucleotide-competitive RT inhibitors.

Enzyme Catalysis (Cont'd)

Impact of Resistance Mutations on Inhibitor Binding to HIV-1 Integrase

Qi Chen, John K. Buolamwini, Jeremy C. Smith, Aixiu Li, Qin Xu, Xiaolin Cheng, Dongqing Wei [Shanghai Jiao Tong University]

J.Chem. Infor. and Mod. **53**, 3297–3307, 2014.

HIV-1 integrase (IN) is essential for HIV-1 replication, catalyzing two key reaction steps termed 3' processing and strand transfer. Therefore, IN has become an important target for antiviral drug discovery. However, mutants have emerged, such as E92Q/N155H and G140S/Q148H, which confer resistance to raltegravir (RAL), the first IN strand transfer inhibitor (INSTI) approved by the FDA, and to the recently approved elvitegravir (EVG). To gain insights into the molecular mechanisms of ligand binding and drug resistance, we performed molecular dynamics (MD) simulations of homology models of the HIV-1 IN and four relevant mutants complexed with viral DNA and RAL.

Molecular Dynamic Investigations of the Mutational Effects on Structural Characteristics and Tunnel Geometry in CYP17A1

Ying-Lu Cui, Qing-Chuan Zheng, Ji-Long Zhang, Qiao Xue, Yan Wang, Hong-Xing Zhang [Jilin University]

J.Chem. Infor. and Mod. **53**, 3308–3317, 2014.

Despite the ample experimental mutagenesis data, the molecular origin and the structural motifs for the enzymatic activities deficiencies have not been rationalized at the atomic resolution. To this end, we have investigated the effects on structural characteristics and tunnel geometry upon single point mutations in CYP17A1. The MD simulation results combined with PMF calculations and MM-GBSA calculations render an “access mechanism” which encapsulates the effects of mutations on the changes in both structural flexibility and tunnel dynamics, bridging the gap between the theory and the experimentally observed results of enzymatic activity decrease.

Virtual Screening of PRK1 Inhibitors: Ensemble Docking, Rescoring Using Binding Free Energy Calculation and QSAR Model Development

Inna Slynko, Michael Scharfe, Tobias Rumpf, Julia Eib, Eric Metzger, Roland Schüle, Manfred Jung, Wolfgang Sippl [Institute of Pharmacy, MLU Halle-Wittenberg]

J.Chem. Infor. and Mod. **54**, 138–150, 2014.

Protein kinase C Related Kinase 1 (PRK1) has been shown to be involved in the regulation of androgen receptor signaling and has been identified as a novel potential drug target for prostate cancer therapy. Since there is no PRK1 crystal structure available to date, multiple PRK1 homology models were generated in order to address the protein flexibility. An in-house library of compounds tested on PRK1 was docked into the ATP binding site of the generated models. In most cases a correct pose of the inhibitors could be identified by ensemble docking, while there is still a challenge of finding a reasonable scoring function that is able to rank compounds according to their biological activity.

Enzyme Catalysis (Cont'd)

Enolization as an Alternative Proton Delivery Pathway in Human Aromatase (P450 19A1)

Balázs Krámos , Julianna Oláh [Budapest University of Technology and Economics]

J. Phys. Chem. B., **118**, 390–405, 2014.

A!

Human aromatase catalyzes the last step of estrogen biosynthesis, the aromatization of ring A of androstenedione (ASD) and testosterone leading to estrone and estradiol. The enolization of the substrate molecule has been suggested to play an essential role in this process. In this work using quantum mechanical and hybrid QM/MM calculations, the reaction mechanism of enolization was investigated. It is shown that the energetically unfavorable enolization of androstenedione occurs in a coupled process with the energetically favorable protonation of the ferrous superoxo complex (traditionally called ferric peroxo complex) via a low barrier of about 5 kcal/mol.

Computational Evaluations of Charge Coupling and Hydrogen Bonding in the Active Site of a Family 7 Cellobiohydrolase

David M. Granum, Shubham Vyas, Somiseti V. Sambasivarao, C. Mark Maupin [Colorado School of Mines]

J. Phys. Chem. B., **118**, 434–448, 2014.

Solution pH and the pK_a values of ionizable residues are critical factors known to influence enzyme catalysis, structural stability, and dynamical fluctuations. Presented here is an exhaustive computational study utilizing long time constant pH molecular dynamics, pH replica exchange simulations, and kinetic modeling to evaluate pH-dependent conformations, charge dynamics, residue pK_a values, and the catalytic activity–pH profile for cellobiohydrolase Cel7B from *Melanocarpus albomyces*. The predicted pK_a values support the role of Glu212 as the catalytic nucleophile and Glu217 as the acid–base residue. The presence of a charge-correlated active site and an extensive hydrogen bonding network is found to be critical in enabling favorable residue orientations for catalysis and shuttling excess protons around the active site.

Computational Studies of the Regioselectivities of COMT-Catalyzed *Meta*-/*Para*-O Methylations of Luteolin and Quercetin

Yang Cao, Zhong-Jian Chen, Hui-Di Jiang, Jian-Zhong Chen [Zhejiang University]

J. Phys. Chem. B., **118**, 470–481, 2014.

Catechol-*O*-methyltransferase (COMT, EC 2.1.1.6) plays a central role in the inactivation of neurotransmitters sharing a catecholic motif by transferring a methyl group from AdoMet. Methylation of the *meta*-hydroxyl is much more common than that of the *para*-hydroxyl in many COMT substrates, such as dopamine and norepinephrine. Our experimental data showed that quercetin preferred *meta*-methylation but luteolin favored a *para*-methylation. To elucidate the mechanism for different preferences of methylations of quercetin and luteolin, we performed a theoretical investigation on the different regioselectivities of COMT-catalyzed methylations for quercetin and luteolin by a combined approach of MD simulations, *ab initio* calculations, and QM/MM computations.

Enzyme Catalysis (Cont'd)

Model Study Using Designed Selenopeptides on the Importance of the Catalytic Triad for the Antioxidative Functions of Glutathione Peroxidase

Toshiki Takei, Yoshiko Urabe, Yuya Asahina, Hironobu Hojo, Takeshi Nomura, Kenichi Dedachi, Kenta Arai, Michio Iwaoka [Tokai University]

J. Phys. Chem. B., **118**, 492–500, 2014.

Although the catalytic triad of glutathione peroxidase (GPx) has been well recognized, there was little evidence for the relevance of the interactions among the triad amino acid residues, i.e., selenocysteine (U), glutamine (Q), and tryptophan (W), to the GPx antioxidative functions. Using a designed selenopeptide having an amino acid sequence of GQAUAWG, we demonstrate here that U, Q, and W present at the active site can interact with each other to exert the enzymatic activity. The amino acid sequence was chosen on the basis of the Monte Carlo molecular simulation for various selenopeptides in polarizable continuous water using the SAAP force field (SAAP-MC).

Proton Transport in *Clostridium pasteurianum* [FeFe] Hydrogenase I: A Computational Study

Hai Long [National Renewable Energy Laboratory], Paul W. King, Christopher H. Chang

J. Phys. Chem. B., **118**, 890–900, 2014.

To better understand the proton transport through the H₂ production catalysts, the [FeFe] hydrogenases, we have undertaken a modeling and simulation study of the proton transfer processes mediated by amino acid side-chain residues in hydrogenase I from *Clostridium pasteurianum*. Free-energy calculation studies show that the side chains of two conserved glutamate residues, Glu-279 and Glu-282, each possess two stable conformations with energies that are sensitive to protonation state.

Molecular Dynamics Simulation Studies on the Positive Cooperativity of the Kemptide Substrate with Protein Kinase A Induced by the ATP Ligand

Chaoqun Li, Na Ma, Yaru Wang, Yan Wang, Guangju Chen [Beijing Normal University]

J. Phys. Chem. B., **118**, 1273–1287, 2014.

The positive cooperativity of the Kemptide substrate or the ATP molecule with the PKA catalytic subunit has been studied by dynamics simulations and free energy calculations on a series of binary and ternary models. The results revealed that the first ATP binding to the PKA catalytic subunit is energetically favorable for the successive Kemptide binding, confirming the positive cooperativity. The key residues Thr51, Glu170, and Phe187 in PKA contributing to the positive cooperativity have been found.

Protein-Protein Interactions

Functional module identification in protein interaction networks by interaction patterns

Yijie Wang [University of South Florida], Xiaoning Qian

Bioinformatics. **30**, 81-93, 2014.

Identifying functional modules in protein-protein interaction (PPI) networks may shed light on cellular functional organization and thereafter underlying cellular mechanisms. Many existing module identification algorithms aim to detect densely connected groups of proteins as potential modules. However, based on this simple topological criterion of 'higher than expected connectivity', those algorithms may miss biologically meaningful modules of functional significance, in which proteins have similar interaction patterns to other proteins in networks but may not be densely connected to each other.

Protein-Protein Interactions (Cont'd)

Molecular modeling of protein–protein interaction to decipher the structural mechanism of nonhost resistance in rice

Ranjit Prasad Bahadur [Indian Institute of Technology, Kharagpur] Jolly Basak

J. Biomol. Stru. and Dyn., **32**, 669-681, 2014.

Nonhost resistance (NHR) is the most common and durable form of plant resistance to disease-causing organisms. A successful example of NHR is the cloning of a maize *R* gene *Rxo1* in rice and validating its function in conferring bacterial streak resistance in transgenic rice lines. In order to understand the structural mechanism of NHR in rice, we built the model of the protein–protein interaction between the encoded *Rxo1* (RXO1) and AvrRXO1 (avirulence protein of rice pathogen, *Xanthomonas oryzae* pv. *oryzicola*).

Membrane Proteins and Lipid Peptide Interactions

MemBuilder: a web-based graphical interface to build heterogeneously mixed membrane bilayers for the GROMACS biomolecular simulation program

Mohammad Mehdi Ghahremanpour, Seyed Shahriar Arab[Tarbiat Modares University], Saman Biook Aghazadeh, Jin Zhang, David van der Spoel

Bioinformatics. **30**, 439-441, 2014.

A!

Molecular dynamics (MD) simulations have had a profound impact on studies of membrane proteins during past two decades, but the accuracy of MD simulations of membranes is limited by the quality of membrane models and the applied force fields. Membrane models used in MD simulations mostly contain one kind of lipid molecule. This is far from reality, for biological membranes always contain more than one kind of lipid molecule. Moreover, the lipid composition and their distribution are functionally important.

Atomistic Simulations of Pore Formation and Closure in Lipid Bilayers

W. F. Drew Bennett, Nicolas Sapay, D. Peter Tieleman [University of Calgary]

Biophysical Journal. **106**, 210-219, 2014.

Cellular membranes separate distinct aqueous compartments, but can be breached by transient hydrophilic pores. A large energetic cost prevents pore formation, which is largely dependent on the composition and structure of the lipid bilayer. The softness of bilayers and the disordered structure of pores make their characterization difficult. We use molecular-dynamics simulations with atomistic detail to study the thermodynamics, kinetics, and mechanism of pore formation and closure in DLPC, DMPC, and DPPC bilayers, with pore formation free energies of 17, 45, and 78 kJ/mol, respectively.

The Molecular Structure of the Liquid-Ordered Phase of Lipid Bilayers

Alexander J. Sodt, Michael Logan Sandar, Klaus Gawrisch, Richard W. Pastor, and Edward Lyman [University of Delaware]

J. Am. Chem. Soc., **136**, 725–732, 2014.

A!

MD simulations reveal substructures within the liquid-ordered phase of lipid bilayers. These substructures, identified in a 10 μ s all-atom trajectory of liquid-ordered/liquid-disordered coexistence (L_o/L_d) are composed of saturated hydrocarbon chains packed with local hexagonal order and separated by interstitial regions enriched in cholesterol and unsaturated chains. Lipid hydrocarbon chain order parameters calculated from the L_o phase are in excellent agreement with ^2H NMR measurements; the local hexagonal packing is also consistent with ^1H -MAS NMR spectra of the L_o phase, NMR diffusion experiments, and small-angle X-ray and neutron scattering.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

How well does cholesteryl hemisuccinate mimic cholesterol in saturated phospholipid bilayers?

Waldemar Kulig, Joonas Tynkkynen, Matti Javanainen, Moutusi Manna, Tomasz Rog, Ilpo Vattulainen, Pavel Jungwirth [Tampere University of Technology]

J. Mol. Mod., **20**, 20:2121, 2014.

Cholesteryl hemisuccinate is a detergent that is often used to replace cholesterol in crystallization of membrane proteins. Here we employ atomistic molecular dynamics simulations to characterize how well the properties of cholesteryl hemisuccinate actually match those of cholesterol in saturated protein-free lipid membranes. We show that the protonated form of cholesteryl hemisuccinate mimics many of the membrane properties of cholesterol quite well, while the deprotonated form of cholesteryl hemisuccinate is less convincing in this respect.

Small molecule interaction with lipid bilayers: A molecular dynamics study of chlorhexidine

Brad Van Oosten [Brock University], Drew Marquardt, Ivana Komljenović, Jeremy P. Bradshaw, Edward Sternin, Thad A. Harroun

J. Mol. Graph. and Mod., **48**, 96-104, 2014.

Chlorhexidine (CHX) is an effective anti-bacterial agent whose mode of action is thought to be the disruption of the cell membrane. We tested the capability of the Slipids all atom force fields using data from neutron scattering and NMR experiments on the drug chlorhexidine in a 1,2-dimyrisoyl-3-*sn*-phosphatidylcholine (DMPC) membrane. Since it is not known what the charge of the CHX molecule is inside an apolar environment, a neutral, as well as a +1 and +2 charge model for the molecule were created and tested at several concentrations.

A!

Engineering Antimicrobial Peptides with Improved Antimicrobial and Hemolytic Activities

Jun Zhao, Chao Zhao, Guizhao Liang, Mingzhen Zhang, Jie Zheng [The University of Akron]

J. Chem. Infor. and Mod. **53**, 3280–3296, 2014.

The rapid rise of antibiotic resistance in pathogens becomes a serious and growing threat to medicine and public health. Naturally occurring antimicrobial peptides (AMPs) are an important line of defense in the immune system against invading bacteria and microbial infection. We used the MARTINI coarse-grained molecular dynamics with adaptive biasing force method and the umbrella sampling technique to investigate the translocation of a total of 91 peptides with different amino acid substitutions through a mixed anionic POPE/POPG (3:1) bilayer and a neutral POPC bilayer, which mimic the bacterial inner membrane and the human red blood cell (hRBC) membrane, respectively.

CSBB-ConeExclusion, Adapting Structure Based Solution Virtual Screening to Libraries on Solid Support

Steven Shave, Manfred Auer [University of Edinburgh]

J. Chem. Infor. and Mod. **53**, 3156–3162, 2014.

Combinatorial chemical libraries produced on solid support offer fast and cost-effective access to a large number of unique compounds. If such libraries are screened directly on-bead, the speed at which chemical space can be explored by chemists is much greater than that addressable using solution based synthesis and screening methods. Solution based screening has a large supporting body of software such as structure-based virtual screening tools which enable the prediction of protein–ligand complexes. Use of these techniques to predict the protein bound complexes of compounds synthesized on solid support neglects to take into account the conjugation site on the small molecule ligand.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Functional Motions Modulating VanA Ligand Binding Unraveled by Self-Organizing Maps

Guillaume Bouvier, Nathalie Duclert-Savatier, Nathan Desdouts, Djalal Meziane-Cherif, Arnaud Blondel, Patrice Courvalin, Michael Nilges, Thérèse E. Malliavin [Institut Pasteur]

J.Chem. Infor. and Mod. **54**, 289–301, 2014.

The VanA d-Ala:d-Lac ligase is a key enzyme in the emergence of high level resistance to vancomycin in *Enterococcus* species and methicillin-resistant *Staphylococcus aureus*. The aim of the present work was (i) to investigate the conformational transition of VanA associated with the opening of its ω -loop and of a part of its central domain and (ii) to relate this transition with the substrate or product binding propensities. Molecular dynamics trajectories of the VanA ligase of *Enterococcus faecium* with or without a disulfide bridge distant from the catalytic site revealed differences in the catalytic site conformations with a slight opening.

Characterizing the binding of annexin V to a lipid bilayer using molecular dynamics simulations

Zhuxi Chen, Yanyan Mao, Jing Yang, Tao Zhang, Lifan Zhao, Kunqian Yu, Mingyue Zheng, Hualiang Jiang, Huaiyu Yang [Chinese Academy of Sciences]

Proteins: Stru. Fun. & Bioinf., **82**, 312–322, 2014.

Here, using long-time molecular dynamics simulations, we provide detailed information for the binding of an annexin V trimer to a POPC/POPS lipid bilayer. Calcium ions function as bridges between several negatively charged residues of annexin V and the oxygen atoms of lipids. The preferred calcium-bridges are those formed via the carboxyl oxygen atoms of POPS lipids. H-bonds and hydrophobic interactions formed by several critical residues have also been observed in the annexin-membrane interface.

A!

Global fold of human cannabinoid type 2 receptor probed by solid-state ^{13}C -, ^{15}N -MAS NMR and molecular dynamics simulations

Tomohiro Kimura, Krishna Vukoti, Diane L. Lynch, Dow P. Hurst, Alan Grossfield, Michael C. Pitman, Patricia H. Reggio, Alexei A. Yeliseev, Klaus Gawrisch [Laboratory of Membrane Biochemistry and Biophysics, NIAAA]

Proteins: Stru. Fun. & Bioinf., **82**, 452–465, 2014.

The global fold of human cannabinoid type 2 (CB_2) receptor in the agonist-bound active state in lipid bilayers was investigated by solid-state ^{13}C - and ^{15}N magic-angle spinning (MAS) NMR, in combination with chemical-shift prediction from a structural model of the receptor obtained by microsecond-long molecular dynamics (MD) simulations. Uniformly ^{13}C - and ^{15}N -labeled CB_2 receptor was expressed in milligram quantities by bacterial fermentation, purified, and functionally reconstituted into liposomes. ^{13}C MAS NMR spectra were recorded without sensitivity enhancement for direct comparison of C_α , C_β , and $\text{C}=\text{O}$ bands of superimposed resonances with predictions from protein structures generated by MD.

Molecular Dynamics Studies of Liposomes as Carriers for Photosensitizing Drugs: Development, Validation, and Simulations with a Coarse-Grained Model

Joakim P. M. Jämbeck, Emma S. E. Eriksson, Aatto Laaksonen, Alexander P. Lyubartsev, Leif A. Eriksson [University of Gothenburg]

J. Chem. Theor. and Comp., **10**, 5–13, 2014.

Liposomes are proposed as drug delivery systems and can in principle be designed so as to cohere with specific tissue types or local environments. Little detail is known about the exact mechanisms for drug delivery and the distributions of drug molecules inside the lipid carrier. In the current work, a coarse-grained (CG) liposome model is developed, consisting of over 2500 lipids, with varying degrees of drug loading. For the drug molecule, we chose hypericin, a natural compound proposed for use in photodynamic therapy, for which a CG model was derived and benchmarked against corresponding atomistic membrane bilayer model simulations.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Calculation of Lipid-Bilayer Permeabilities Using an Average Force

Jeffrey Comer, Klaus Schulten, Christophe Chipot
[University of Illinois at Urbana-Champaign]

J. Chem. Theor. and Comp., **10**, 554–564, 2014.

Calculations of lipid bilayer permeabilities from first principles, using molecular simulations, would be valuable to rapidly assess the bioavailability of drug candidates, as well as to decipher, at the atomic level, the mechanisms that underlie the translocation of permeants. In the present work, we combine importance-sampling simulations employing an adaptive biasing force with a Bayesian-inference algorithm to determine the free energy and diffusivity with noteworthy precision and spatial resolution.

Importance of Force Decomposition for Local Stress Calculations in Biomembrane Molecular Simulations

Juan M. Vanegas, Alejandro Torres-Sánchez, Marino Arroyo
[Universitat Politècnica de Catalunya-BarcelonaTech]

J. Chem. Theor. and Comp., **10**, 691–702, 2014.

Local stress fields are routinely computed from molecular dynamics trajectories to understand the structure and mechanical properties of lipid bilayers. These calculations can be systematically understood with the Irving–Kirkwood–Noll theory. Here, we present a new implementation of local stress calculations that systematically treats constraints and considers a privileged decomposition, the central force decomposition, that leads to a symmetric stress tensor by construction.

Lipid14: The Amber Lipid Force Field

Callum J. Dickson, Benjamin D. Madej, Åge A. Skjevik, Robin M. Betz, Knut Teigen, Ian R. Gould [Imperial College London], Ross C. Walker

J. Chem. Theor. and Comp., **10**, 865–879, 2014.

The AMBER lipid force field has been updated to create Lipid14, allowing tensionless simulation of a number of lipid types with the AMBER MD package. The modular nature of this force field allows numerous combinations of head and tail groups to create different lipid types, enabling the easy insertion of new lipid species. The Lennard-Jones and torsion parameters of both the head and tail groups have been revised and updated partial charges calculated.

Effect of PEGylation on Drug Entry into Lipid Bilayer

Sami Rissanen, Marta Kumorek, Hector Martinez-Seara, Yen-Chin Li, Dorota Jamróz, Alex Bunker, Maria Nowakowska, Ilpo Vattulainen, Mariusz Kepczynski, Tomasz Róg[Tampere University of Technology]

J. Phys. Chem. B., **118**, 144–151, 2014.

Poly(ethylene glycol) (PEG) is a polymer commonly used for functionalization of drug molecules to increase their bloodstream lifetime, hence efficacy. However, the interactions between the PEGylated drugs and biomembranes are not clearly understood. In this study, we employed atomic-scale molecular dynamics (MD) simulations to consider the behavior of two drug molecules functionalized with PEG (tetraphenylporphyrin used in cancer phototherapy and biochanin A belonging to the isoflavone family) in the presence of a lipid bilayer.

Protein Folding

The role of Cys179–Cys214 disulfide bond in the stability and folding of prion protein: insights from molecular dynamics simulations

Lulu Ning, Jingjing Guo, Nengzhi Jin, Huanxiang Liu, Xiaojun Yao [Lanzhou University]

J. Mol.Mod., **20**, 20:2106, 2014.

Prion diseases are associated with misfolding and aggregation of prion protein (PrP). Cellular prion protein contains a disulfide bond linking Cys residues at positions 179 and 214. It has been proposed that this disulfide bond plays an important role in the conversion between cellular (PrP^C) and the scrapie form of prion protein (PrP^{Sc}). To probe the role of this disulfide bond in the stability and folding of prion protein, we employed molecular dynamics simulations to study the reduced prion protein and a variant of PrP in which the two cysteines were replaced by alanines residues.

Design of a Rotamer Library for Coarse-Grained Models in Protein-Folding Simulations

María Larriva ,Antonio Rey [Universidad Complutense]

J.Chem. Infor. and Mod. **54**, 302–313, 2014.

We have dispensed with an atomic description of proteins, representing each amino acid side chain by its geometric center (or centroid). The resulting rotamers have been estimated from a statistical analysis of a large structural database consisting of high-resolution X-ray protein structures. As additional information, each rotamer includes the frequency with which it has been found during the statistical analysis. More importantly, the library has been designed with a careful control to ensure that the vast majority of side chains in protein structures (at least 95% of residues) are properly represented.

Designing cooperativity into the designed protein Top7

Shilpa Yadahalli ,Shachi Gosavi [Tata Institute of Fundamental Research, Bangalore]

Proteins: Stru. Fun. & Bioinf., **82**, 364–374, 2014.

The topology of the designed protein Top7 is not found in natural proteins. Top7 shows signatures of non-cooperative folding in both experimental studies and computer simulations. In particular, molecular dynamics of coarse-grained structure-based models of Top7 show a well-populated C-terminal folding-intermediate. Since most similarly sized globular proteins are cooperative folders, the non-natural topology of Top7 has been suggested as a reason for its non-cooperative folding. Here, we computationally examine the folding of Top7 with the intent of making it cooperative.

Folding 19 proteins to their native state and stability of large proteins from a coarse-grained model

Abhijeet Kapoor [Iowa State University] ,Alex Travesse

Proteins: Stru. Fun. & Bioinf., **82**, 505–516, 2014.

We develop an intermediate resolution model, where the backbone is modeled with atomic resolution but the side chain with a single bead, by extending our previous model (*Proteins* (2013) DOI: 10.1002/prot.24269) to properly include proline, preproline residues and backbone rigidity. Starting from random configurations, the model properly folds 19 proteins (including a mutant 2A3D sequence) into native states containing β sheet, α helix, and mixed α/β . As a further test, the stability of H-RAS (a 169 residue protein, critical in many signaling pathways) is investigated: The protein is stable, with excellent agreement with experimental B-factors.

Protein-Nucleic acid Interactions

Development of purely structure-based pharmacophores for the topoisomerase I-DNA-ligand binding pocket

Malgorzata N. Drwal, Keli Agama, Yves Pommier, Renate Griffith [University of New South Wales]

J. Comp. Aided. Mol. Design, **27**, 1037-1049, 2014.

A!

Purely structure-based pharmacophores (SBPs) are an alternative method to ligand-based approaches and have the advantage of describing the entire interaction capability of a binding pocket. Here, we present the development of SBPs for topoisomerase I, an anticancer target with an unusual ligand binding pocket consisting of protein and DNA atoms. Different approaches to cluster and select pharmacophore features are investigated, including hierarchical clustering and energy calculations. In addition, the performance of SBPs is evaluated retrospectively and compared to the performance of ligand- and complex-based pharmacophores.

RESPAC: Method to Determine Partial Charges in Coarse-Grained Protein Model and Its Application to DNA-Binding Proteins

Tsuyoshi Terakawa, Shoji Takada [Kyoto University]

J. Chem. Theor. and Comp, **10**, 711–721, 2014.

A!

While coarse-grained (CG) molecular simulations for large biomolecular complexes have become popular, their electrostatic treatment is often rather simplistic. Here, for C_α -based CG models of globular proteins, we developed a method to obtain an optimal partial charge set and applied it to 17 proteins that bind to DNA. The method follows the restrained electrostatic potential (RESP) fitting method widely used for determination of atomic partial charges in all-atom (AA) molecular mechanics.

Photophysical and Dynamical Properties of Doubly Linked Cy3–DNA Constructs

Elana M. S. Stennett, Ning Ma, Arjan van der Vaart, Marcia Levitus [Arizona State University]

J. Phys. Chem. B., **118**, 152–163, 2014.

Photophysical measurements are reported for Cy3–DNA constructs in which both Cy3 nitrogen atoms are attached to the DNA backbone by short linkers. While this linking was thought to rigidify the orientation of the dye and hinder *cis*-isomerization, the relatively low fluorescence quantum yield and the presence of a short component in the time-resolved fluorescence decay of the dye indicated that *cis*-isomerization remained possible. Fluorescence correlation spectroscopy and transient absorption experiments showed that photoisomerization occurred with high efficiency.

Choline Ion Interactions with DNA Atoms Explain Unique Stabilization of A–T Base Pairs in DNA Duplexes: A Microscopic View

Miki Nakano, Hisae Tateishi-Karimata, Shigenori Tanaka, Naoki Sugimoto [Konan University]

J. Phys. Chem. B., **118**, 379–389, 2014.

Under physiological conditions, G–C base pairs are more stable than A–T base pairs. In a previous study, we showed that in the hydrated ionic liquid of choline dihydrogen phosphate, the stabilities of these base pairs are reversed. In the present study, we elucidated the unique binding interactions of choline ions with DNA atoms from a microscopic viewpoint using molecular dynamics simulations. Three times more choline ions bind to the DNA duplex than sodium ions. Sodium ions bind closely but not stably; in contrast, the choline ions bind through multiple hydrogen bonding networks with DNA atoms stably.

Protein-Nucleic Acid Interactions (Cont'd)

Molecular Dynamics of DNA-Protein Conjugates on Electrified Surfaces: Solutions to the Drift-Diffusion Equation

A. Langer, W. Kaiser, M. Svejda, P. Schwertler, U. Rant
[Technische Universität München]

J. Phys. Chem. B., **118**, 597–607, 2014.

Self-assembled monolayers of charged polymers are an integral component of many state-of-the-art nanobiosensors. Electrical interactions between charged surfaces and charged biomolecules, adopting the roles of linkers or capture molecules, are not only crucial to the sensor performance but may also be exploited for novel sensing concepts based on electrically actuated interfaces. Here we introduce an analytical model describing the behavior of double-stranded DNA and proteins tethered to externally biased microelectrodes.

Nucleic Acids

snoStrip: a snoRNA annotation pipeline

Sebastian Bartschat [University of Leipzig], Stephanie Kehr, Hakim Tafer, Peter F. Stadler, Jana Hertel

Bioinformatics. **30**, 115–116, 2014.

Although small nucleolar RNAs form an important class of non-coding RNAs, no comprehensive annotation efforts have been undertaken, presumably because the task is complicated by both the large number of distinct small nucleolar RNA families and their relatively rapid pace of sequence evolution. With *snoStrip* we present an automatic annotation pipeline developed specifically for comparative genomics of small nucleolar RNAs.

Docking Studies on DNA Intercalators

Yocheved Gilad [Bar Ilan University], Hanoch Senderowitz

J. Chem. Infor. and Mod. **54**, 96–107, 2014.

DNA is an important target for the treatment of multiple pathologies, most notably cancer. In particular, DNA intercalators have often been used as anticancer drugs. However, despite their relevance to drug discovery, only a few systematic computational studies were performed on DNA-intercalator complexes. In this work we have analyzed ligand binding site preferences in 63 high resolution DNA-intercalator complexes available in the PDB and found that ligands bind preferentially between **G** and **C** and between the **C** and **A** base pairs (70% and 11%, respectively). Next, we examined the ability of AUTODOCK to accurately dock ligands into preformed intercalation sites.

Energies and 2'-Hydroxyl Group Orientations of RNA Backbone Conformations. Benchmark CCSD(T)/CBS Database, Electronic Analysis, and Assessment of DFT Methods and MD Simulations

Arnošt Mládek, Pavel Banáš, Petr Jurečka, Michal Otyepka, Marie Zgarbová, Jiří Šponer [Academy of Sciences of the Czech Republic]

J. Chem. Theor. and Comp., **10**, 463–480, 2014.

Sugar-phosphate backbone is an electronically complex molecular segment imparting RNA molecules high flexibility and architectonic heterogeneity necessary for their biological functions. The structural variability of RNA molecules is amplified by the presence of the 2'-hydroxyl group, capable of forming multitude of intra- and intermolecular interactions. Bioinformatics studies based on X-ray structure database revealed that RNA backbone samples at least 46 substates known as rotameric families. The present study provides a comprehensive analysis of RNA backbone conformational preferences and 2'-hydroxyl group orientations.

Nucleic Acids (Cont'd)

Are Waters around RNA More than Just a Solvent? – An Insight from Molecular Dynamics Simulations

Petra Kührová, Michal Otyepka, Jiří Šponer, Pavel Banáš [Palacky University]

J. Chem. Theor. and Comp., **10**, 401–411, 2014.

Hydrating water molecules are believed to be an inherent part of the RNA structure and have a considerable impact on RNA conformation. However, the magnitude and mechanism of the interplay between water molecules and the RNA structure are still poorly understood. In principle, such hydration effects can be studied by molecular dynamics (MD) simulations. In our recent MD studies, we observed that the choice of water model has a visible impact on the predicted structure and structural dynamics of RNA and, in particular, has a larger effect than type, parametrization, and concentration of the ions.

Multidimensional Replica Exchange Molecular Dynamics Yields a Converged Ensemble of an RNA Tetranucleotide

Christina Bergonzo, Niel M. Henriksen, Daniel R. Roe, Jason M. Swails, Adrian E. Roitberg, Thomas E. Cheatham, III [University of Utah]

J. Chem. Theor. and Comp., **10**, 492–499, 2014.

Given questions regarding the reliability of modeling RNA structure and dynamics with current methods, we have begun to use RNA tetranucleotides to evaluate force fields. These systems, though small, display considerable conformational variability and complete sampling with standard simulation methods remains challenging. Here we compare and discuss the performance of known variations of replica exchange molecular dynamics (REMD) methods, specifically temperature REMD (T-REMD), Hamiltonian REMD (H-REMD), and multidimensional REMD (M-REMD) methods, which have been implemented in Amber's accelerated GPU code.

Benchmarking the Electron Affinity of Uracil

Jiande Gu, Yaoming Xie, Henry F. Schaefer [University of Georgia]

J. Chem. Theor. and Comp., **10**, 609–612, 2014.

The Weizmann Bruecker doubles composite method W1BD has been applied in a benchmark study of electron attachment to the nucleobase uracil. The largest computations involved the BD method with a basis set of 760 contracted Gaussian functions, namely augh-cc-pVQZ+2df. The predictions demonstrate that the adiabatic electron affinity (AEA) of uracil is definitely positive. The most reliable value for the AEA of uracil should be 0.024 ± 0.013 eV. Other high level methods such as CASPT2 and G4 theory also predict the AEA of uracil with reasonable accuracy.

Optimization of an AMBER Force Field for the Artificial Nucleic Acid, LNA, and Benchmarking with NMR of L(CAAU)

David E. Condon, Ilyas Yildirim, Scott D. Kennedy, Brendan C. Mort, Ryszard Kierzek, Douglas H. Turner [University of Rochester]

J. Phys. Chem. B., **118**, 1216–1228, 2014.

Locked Nucleic Acids (LNAs) are RNA analogues with an O2'-C4' methylene bridge which locks the sugar into a C3'-endo conformation. This enhances hybridization to DNA and RNA, making LNAs useful in microarrays and potential therapeutics. Here, the LNA, L(CAAU), provides a simplified benchmark for testing the ability of molecular dynamics (MD) to approximate nucleic acid properties. LNA χ torsions and partial charges were parametrized to create AMBER parm99_LNA. The revisions were tested by comparing MD predictions with AMBER parm99 and parm99_LNA against a 200 ms NOESY NMR spectrum of L(CAAU). NMR indicates an A-Form equilibrium ensemble.

Surfaces, Catalysts, and Materials Subjects

CHARMM36 United Atom Chain Model for Lipids and Surfactants

Sarah Lee, Alan Tran, Matthew Allsopp, Joseph B. Lim, Jérôme Hénin, Jeffery B. Klauda [University of Maryland]

J. Phys. Chem. B., **118**, 547–556, 2014.

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Molecular simulations of lipids and surfactants require accurate parameters to reproduce and predict experimental properties. Previously, a united atom (UA) chain model was developed for the CHARMM27/27r lipids (Hénin, J., et al. *J. Phys. Chem. B.* **2008**, *112*, 7008–7015) but suffers from the flaw that bilayer simulations using the model require an imposed surface area ensemble, which limits its use to pure bilayer systems. A UA-chain model has been developed based on the CHARMM36 (C36) all-atom lipid parameters, termed C36-UA, and agreed well with bulk, lipid membrane, and micelle formation of a surfactant. Molecular dynamics (MD) simulations of alkanes (heptane and pentadecane) were used to test the validity of C36-UA on density, heat of vaporization, and liquid self-diffusion constants.

2. METHODOLOGY

Quantitative Structure-Activity Relations

A highly predictive 3D-QSAR model for binding to the voltage-gated sodium channel: Design of potent new ligands

Congxiang Zha, George B. Brown, Wayne J. Brouillette [The University of Alabama at Birmingham]

Bioorg. and Med.Chem., **22**, 95-104, 2014.

A comprehensive comparative molecular field analysis (CoMFA) model for the binding of ligands to the neuronal voltage-gated sodium channel was generated based on 67 diverse compounds. Earlier published CoMFA models for this target provided μM ligands, but the improved model described here provided structurally novel compounds with low nM IC_{50} . For example, new compounds **94** and **95** had IC_{50} values of 129 and 119 nM, respectively.

Data Set Modelability by QSAR

Alexander Golbraikh, Eugene Muratov, Denis Fourches, Alexander Tropsha [University of North Carolina]

J.Chem. Infor. and Mod. **54**, 1–4, 2014.

We introduce a simple MODelability Index (MODI) that estimates the feasibility of obtaining predictive QSAR models (correct classification rate above 0.7) for a binary data set of bioactive compounds. MODI is defined as an activity class-weighted ratio of the number of nearest-neighbor pairs of compounds with the same activity class versus the total number of pairs. The MODI values were calculated for more than 100 data sets, and the threshold of 0.65 was found to separate the nonmodelable and modelable data sets.

Quantitative Structure-Activity Relations (Cont'd)

Binary Classification of a Large Collection of Environmental Chemicals from Estrogen Receptor Assays by Quantitative Structure-Activity Relationship and Machine Learning Methods

Qingda Zang, Daniel M. Rotroff, Richard S. Judson [U.S. Environmental Protection Agency]

J.Chem. Infor. and Mod. **53**, 3244–3261, 2014.

There are thousands of environmental chemicals subject to regulatory decisions for endocrine disrupting potential. The ToxCast and Tox21 programs have tested ~8200 chemicals in a broad screening panel of in vitro high-throughput screening (HTS) assays for estrogen receptor (ER) agonist and antagonist activity. The present work uses this large data set to develop in silico quantitative structure-activity relationship (QSAR) models using machine learning (ML) methods and a novel approach to manage the imbalanced data distribution.

Potentials and Parameters

Development and use of an atomistic CHARMM-based forcefield for peptoid simulation

Dina T. Mirijanian, Ranjan V. Mannige, Ronald N. Zuckermann and Stephen Whitelam [Lawrence Berkeley National Laboratory]

J. Comp. Chem., **35**, 360–370, 2014.

Peptoids are positional isomers of peptides: peptoid sidechains are attached to backbone nitrogens rather than α -carbons. We present a first-generation atomistic forcefield for peptoids. Our forcefield is based on the peptide forcefield CHARMM22, with key parameters tuned to match both experimental data and quantum mechanical calculations for two model peptoids (dimethylacetamide and a sarcosine dipeptoid). We used this forcefield to demonstrate that solvation of a dipeptoid substantially modifies the conformations it can access.

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Predicting Drug-Target Interactions Using Probabilistic Matrix Factorization

Murat Can Cobanoglu, Chang Liu, Feizhuo Hu, Zoltán N. Oltvai, Ivet Bahar [University of Pittsburgh]

J.Chem. Infor. and Mod. **53**, 3399–3409, 2014.

In the present study, we present a method that uses probabilistic matrix factorization (PMF) for this purpose, which is particularly useful for analyzing large interaction networks. DrugBank drugs clustered based on PMF latent variables show phenotypic similarity even in the absence of 3D shape similarity. Benchmarking computations show that the method outperforms those recently introduced provided that the input data set of known interactions is sufficiently large—which is the case for enzymes and ion channels, but not for G-protein coupled receptors (GPCRs) and nuclear receptors.

Modeling Complex Metabolic Reactions, Ecological Systems, and Financial and Legal Networks with MIANN Models Based on Markov-Wiener Node Descriptors

Aliuska Duardo-Sánchez, Cristian R. Munteanu [University of A Coruña], Pablo Riera-Fernández, Antonio López-Díaz, Alejandro Pazos, Humberto González-Díaz

J.Chem. Infor. and Mod. **54**, 16–29, 2014.

The use of numerical parameters in Complex Network analysis is expanding to new fields of application. At a molecular level, we can use them to describe the molecular structure of chemical entities, protein interactions, or metabolic networks. However, the applications are not restricted to the world of molecules and can be extended to the study of macroscopic nonliving systems, organisms, or even legal or social networks. In this work, we explore for the first time the possibility of using Markov chains to calculate analogues of node distance numbers/ W to describe complex networks from the point of view of their nodes.

Molecular Dynamics

C-H...pi interactions in proteins: prevalence, pattern of occurrence, residue propensities, location, and contribution to protein stability

Manjeet Kumar, Petety V. Balaji [Indian Institute of Technology Bombay]

J. Mol.Mod., **20**, 20:2136, 2014.

C-H...pi interactions are a class of non-covalent interactions found in different molecular systems including organic crystals, proteins and nucleic acids. High-resolution protein structures have been analyzed in the present study to delineate various aspects of C-H...pi interactions. Additionally, to determine the extent to which redundancy of a database biases the outcome, two datasets differing from each other in the level of redundancy have been analyzed.

Targeting Histidine Side Chains in Molecular Design through Nitrogen–Halogen Bonds

Andreas Lange, Markus O. Zimmermann, Rainer Wilcken, Stefan Zahn, , Frank M. Boeckler [Eberhard-Karls-University Tübingen]

J.Chem. Infor. and Mod. **53**, 3178–3189, 2014.

Halogen bonds are directional noncovalent interactions that can be used to target electron donors in a protein binding site. In this study, we employ quantum chemical calculations to explore halogen...nitrogen contacts involving histidine side chains. We characterize the energetics on the MP2 level of theory using SCS-MP2 and CCSD(T)/CBS as reference calculations and elucidate their energy profile in suboptimal geometries. We derive simple rules allowing medicinal chemists and chemical biologists to easily determine preferred areas of interaction in a binding site and exploit them for scaffold decoration and design.

On the Application of Good-Turing Statistics to Quantify Convergence of Biomolecular Simulations

Panagiotis I. Koukos , Nicholas M. Glykos [Democritus University of Thrace]

J.Chem. Infor. and Mod. **54**, 209–217, 2014.

Quantifying convergence and sufficient sampling of macromolecular molecular dynamics simulations is more often than not a source of controversy (and of various ad hoc solutions) in the field. Clearly, the only reasonable, consistent, and satisfying way to infer convergence (or otherwise) of a molecular dynamics trajectory must be based on probability theory. Ideally, the question we would wish to answer is the following: “What is the probability that a molecular configuration important for the analysis in hand has not yet been observed?”. Here we propose a method for answering a variant of this question by using the Good-Turing formalism for frequency estimation of unobserved species in a sample.

Docking Ligands into Flexible and Solvated Macromolecules. 6. Development and Application to the Docking of HDACs and other Zinc Metalloenzymes Inhibitors

Joshua Pottel, Eric Therrien, James L. Gleason, Nicolas Moitessier [McGill University]

J.Chem. Infor. and Mod. **54**, 254–265, 2014.

Several members of this class take advantage of the Lewis acidic properties of zinc ions to carry out their various catalytic transformations including isomerization or amide cleavage. These enzymes have been validated as drug targets for a number of diseases including cancer; however, despite their pharmaceutical relevance and the availability of crystal structures, structure-based drug design methods have been poorly and indirectly parametrized for these classes of enzymes. We report herein the development of specific functions and parameters to account for zinc–drug coordination focusing on the above-listed phenomena and their impact on docking to zinc metalloenzymes.

Molecular Dynamics (Cont'd)

Insights on Na⁺ binding and conformational dynamics in multidrug and toxic compound extrusion transporter NorM

Jianing Song, Changge Ji, John Z. H. Zhang [New York University]

Proteins: Stru. Fun. & Bioinf., **82**, 240–249, 2014.

MATE transporter NorM from *Vibrio cholerae* is an antiporter that is driven by Na⁺ gradient to extrude the substrates. To understand the molecular mechanism of Na⁺-substrate exchange, molecular dynamics simulation was performed to study conformational changes of both wild-type and mutant NorM with and without cation bindings. Our results show that NorM is able to bind two Na⁺ ions simultaneously, one to each of the carboxylic groups of E255 and D371 in the binding pocket.

Stabilization of the integrase-DNA complex by Mg²⁺ ions and prediction of key residues for binding HIV-1 integrase inhibitors

Lamia Miri, Guillaume Bouvier, Anass Kettani, Afaf Mikou, Lahcen Wakrim, Michael Nilges and Thérèse E. Malliavin [Institut Pasteur]

Proteins: Stru. Fun. & Bioinf., **82**, 466–478, 2014

The HIV-1 integrase is an attractive target for the therapeutics development against AIDS, as no host homologue of this protein has been identified. The integrase strand transfer inhibitors (INSTIs), including raltegravir, specifically target the second catalytic step of the integration process by binding to the DDE motif of the catalytic site and coordinating Mg²⁺ ions. Recent X-ray crystallographic structures of the integrase/DNA complex from prototype foamy virus allowed to investigate the role of the different partners (integrase, DNA, Mg²⁺ ions, raltegravir) in the complex stability using molecular dynamics (MD) simulations. The presence of Mg²⁺ ions is found to be essential for the stability, whereas the simultaneous presence of raltegravir and Mg²⁺ ions has a destabilizing influence.

Optimizing Protein–Protein van der Waals Interactions for the AMBER ff9x/ff12 Force Field

Dail E. Chapman, Jonathan K. Steck, Paul S. Nerenberg [W. M. Keck Science Department]

J. Chem. Theor. and Comp., **10**, 273–281, 2014.

The quality of molecular dynamics (MD) simulations relies heavily on the accuracy of the underlying force field. In recent years, considerable effort has been put into developing more accurate dihedral angle potentials for MD force fields, but relatively little work has focused on the nonbonded parameters, many of which are two decades old. In this work, we assess the accuracy of protein–protein van der Waals interactions in the AMBER ff9x/ff12 force field.

Highly Scalable and Memory Efficient Ultra-Coarse-Grained Molecular Dynamics Simulations

John. M. A. Grime, Gregory A. Voth [Institute, University of Chicago]

J. Chem. Theor. and Comp., **10**, 423–431, 2014.

The use of coarse-grained (CG) models can significantly increase the time and length scales accessible to computational molecular dynamics (MD) simulations. To address very large-scale phenomena, however, requires a careful consideration of memory requirements and parallel MD load balancing in order to make efficient use of current supercomputers. In this work, a CG-MD code is introduced which is specifically designed for very large, highly parallel simulations of systems with markedly non-uniform particle distributions, such as those found in highly CG models having an implicit solvent.

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Molecular Dynamics (Cont'd)

Molecular Mechanisms for the Reaction Between $\cdot\text{OH}$ Radicals and Proline: Insights on the Role as Reactive Oxygen Species Scavenger in Plant Stress

Santiago Signorelli[Universidad de la República], E. Laura Coitiño, Omar Borsani, Jorge Monza

J. Phys. Chem. B., **118**, 37–47, 2014.

The accumulation of proline (**Pro**) and overproduction of reactive oxygen species (ROS) by plants exposed to stress is well-documented. In vitro assays show that enzyme inactivation by hydroxyl radicals ($\cdot\text{OH}$) can be avoided in the presence of **Pro**, suggesting this amino acid might act as a $\cdot\text{OH}$ scavenger. Although production of hydroxyproline (**Hyp**) has been hypothesized in connection with such antioxidant activity, no evidence on the detailed mechanism of scavenging has been reported. To elucidate whether and how **Hyp** might be produced, we used density functional theory calculations coupled to a polarizable continuum model to explore 27 reaction channels including H-abstraction by $\cdot\text{OH}$ and $\cdot\text{OH}/\text{H}_2\text{O}$ addition.

Difference of Carboxybetaine and Oligo(ethylene glycol) Moieties in Altering Hydrophobic Interactions: A Molecular Simulation Study

Qing Shao, Andrew D. White, Shaoyi Jiang [University of Chicago]

J. Phys. Chem. B., **118**, 189–194, 2014.

Polycarboxybetaine and poly(ethylene glycol) materials resist nonspecific protein adsorption but differ in influencing biological functions such as enzymatic activity. To investigate this difference, we studied the influence of carboxybetaine and oligo(ethylene glycol) moieties on hydrophobic interactions using molecular simulations. We employed a model system composed of two non-polar plates and studied the potential of mean force of plate–plate association in carboxybetaine, (ethylene glycol)₄, and (ethylene glycol)₂ solutions using well-tempered metadynamics simulations.

Accurate Determination of the Orientational Distribution of a Fluorescent Molecule in a Phospholipid Membrane

Štěpán Timr, Alexey Bondar, Lukasz Cwiklik, Martin Štefl, Martin Hof, Mario Vazdar, Josef Lazar, Pavel Jungwirth [Academy of Sciences of the Czech Republic]

J. Phys. Chem. B., **118**, 855–863, 2014.

Orientation of lipophilic dye molecules within a biological membrane can report on the molecular environment, i.e., the physical and chemical properties of the surrounding membrane. This fact, however, remains under-utilized, largely because of our limited quantitative knowledge of molecular orientational distributions and the fact that robust techniques allowing experimental observation of molecular orientations of dyes in biological membranes are only being developed. In order to begin filling this lack of knowledge and to develop appropriate tools, we have investigated the membrane orientational distribution of the 3-hydroxyflavone-based membrane dye F2N12S.

Molecular Dynamics (Cont'd)

Hydroxyl-Proton Hydrogen Bonding in the Heparin Oligosaccharide Arixtra in Aqueous Solution

Consuelo N. Beecher, Robert P. Young, Derek J. Langeslay, Leonard J. Mueller, Cynthia K. Larive [University of California–Riverside]

J. Phys. Chem. B., **118**, 482–491, 2014.

Heparin is best known for its anticoagulant activity, which is mediated by the binding of a specific pentasaccharide sequence to the protease inhibitor antithrombin-III (AT-III). Although heparin oligosaccharides are thought to be flexible in aqueous solution, the recent discovery of a hydrogen bond between the sulfamate (NHSO_3^-) proton and the adjacent 3-*O*-sulfo group of the 3,6-*O*-sulfated *N*-sulfoglucosamine residue of the Arixtra (fondaparinux sodium) pentasaccharide demonstrates that definable elements of local structure are accessed. Molecular dynamics simulations of Arixtra suggest the presence of additional hydrogen bonds involving the C3-OH groups of the glucuronic acid and 2-*O*-sulfo-iduronic acid residues.

Free Energy Perturbation

Quantum Mechanical/Molecular Mechanical Free Energy Simulations of the Self-Cleavage Reaction in the Hepatitis Delta Virus Ribozyme

Abir Ganguly, Pallavi Thaplyal, Edina Rosta, Philip C. Bevilacqua [University Park, Pennsylvania], and Sharon Hammes-Schiffer

J. Am. Chem. Soc., **136**, 1483–1496, 2014.

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The hepatitis delta virus (HDV) ribozyme catalyzes a self-cleavage reaction using a combination of nucleobase and metal ion catalysis. Both divalent and monovalent ions can catalyze this reaction, although the rate is slower with monovalent ions alone. Herein, we use quantum mechanical/molecular mechanical (QM/MM) free energy simulations to investigate the mechanism of this ribozyme and to elucidate the roles of the catalytic metal ion. With Mg^{2+} at the catalytic site, the self-cleavage mechanism is observed to be concerted with a phosphorane-like transition state and a free energy barrier of ~ 13 kcal/mol, consistent with free energy barrier values extrapolated from experimental studies.

Roadmaps through Free Energy Landscapes Calculated Using the Multidimensional vFEP Approach

Tai-Sung Lee[Rutgers University], Brian K. Radak, Ming Huang, Kin-Yiu Wong, Darrin M. York

J. Chem. Theor. and Comp., **10**, 24–34, 2014.

The variational free energy profile (vFEP) method is extended to two dimensions and tested with molecular simulation applications. The proposed 2D-vFEP approach effectively addresses the two major obstacles to constructing free energy profiles from simulation data using traditional methods: the need for overlap in the reweighting procedure and the problem of data representation. This is especially evident as these problems are shown to be more severe in two dimensions. The vFEP method is demonstrated to be highly robust and able to provide stable analytic free energy profiles with only a paucity of sampled data.

Free Energy Perturbation (Cont'd)

Energy-Driven Undocking (EDU-HREM) in Solute Tempering Replica Exchange Simulations

Piero Procacci [Università di Firenze], Marco Bizzarri, Simone Marsili

J. Chem. Theor. and Comp., **10**, 439–450, 2014.

We present a new computational strategy for calculating the absolute binding free energy for protein ligand association in the context of atomistic simulation in explicit solvent. The method is based on an appropriate definition of a solute tempering scheme enforced via Hamilton replica exchange method (HREM). The definition of “solute” includes both the ligand and the active site, with the remainder of the systems defined as “solvent”.

Enhanced Monte Carlo Sampling through Replica Exchange with Solute Tempering

Daniel J. Cole, Julian Tirado-Rives, William L. Jorgensen [Yale University]

J. Chem. Theor. and Comp., **10**, 565–571, 2014.

With a view to improving the consistency of free energy perturbation calculations in Monte Carlo simulations of protein–ligand complexes, we have implemented the replica exchange with solute tempering (REST) method in the *MCPRO* software. By augmenting the standard REST approach with regular attempted jumps in selected dihedral angles, our combined method facilitates sampling of ligand binding modes that are separated by high free energy barriers and ensures that computed free energy changes are considerably less dependent on the starting conditions and the chosen mutation pathway than those calculated with standard Monte Carlo sampling.

QM and QM/MM

Exploring the Aldol Reaction using Catalytic Antibodies and “On Water” Organocatalysts from QM/MM Calculations

Kira Armacost and Orlando Acevedo [Auburn University, Auburn]

J. Am. Chem. Soc., **136**, 147–156, 2014.

The aldol reaction between benzaldehyde and acetone has been investigated using QM/MM Monte Carlo calculations and free-energy perturbation theory to determine the origin of the enhanced rates and enantioselectivities (% ee) derived from an enamine-based catalytic antibody 33F12 and a chiral organocatalyst. Electrostatic stabilization of the general acid/base TyrL36 by TrpH103, SerH100, and AsnL34 enabled the 33F12 active site to exclusively adopt an *si*-face benzaldehyde orientation for C–C bond formation with the LysH93-enamine.

An extensible interface for QM/MM molecular dynamics simulations with AMBER

Andreas W. Götz [University of California San Diego], Matthew A. Clark and Ross C. Walker

J. Comp. Chem., **35**, 95–108, 2014.

We present an extensible interface between the AMBER molecular dynamics (MD) software package and electronic structure software packages for quantum mechanical (QM) and mixed QM and classical molecular mechanical (MM) MD simulations within both mechanical and electronic embedding schemes. With this interface, *ab initio* wave function theory and density functional theory methods, as available in the supported electronic structure software packages, become available for QM/MM MD simulations with AMBER.

QM and QM/MM (Cont'd)

Quantum mechanical investigations on the role of C-terminal residue in influencing the structural features of dipeptides containing N-terminal proline

Gunajyoti Das, Shilpi Mandal [North Eastern Hill University]

J. Mol. Graph. and Mod., **49**, 1-10, 2014.

This study investigates the influence of the side chain moiety of C-terminal residue on the structural and molecular properties of seven dipeptides having proline at their N-terminal positions. The C-terminal component of the dipeptides is varied with seven different combinations viz. Ala, Leu, Asp, Thr, Asn, Arg and Sec. The calculations are carried out using B3LYP/6-311++G(d,p) level of theory in gas and implicit aqueous phase. Effects of explicit aqueous environment on the dipeptide structures are also investigated for two systems.

Halogen Bond: Its Role beyond Drug-Target Binding Affinity for Drug Discovery and Development

Zhijian Xu, Zhuo Yang, Yingtao Liu, Yunxiang Lu [East China University of Science and Technology], Kaixian Chen, and Weiliang Zhu

J. Chem. Infor. and Mod. **54**, 69–78, 2014.

Halogen bond has attracted a great deal of attention in the past years for hit-to-lead-to-candidate optimization aiming at improving drug-target binding affinity. In general, heavy organohalogens (i.e., organochlorines, organobromines, and organoiodines) are capable of forming halogen bonds while organofluorines are not. In order to explore the possible roles that halogen bonds could play beyond improving binding affinity, we performed a detailed database survey and quantum chemistry calculation.

Nonadiabatic Ensemble Simulations of *cis*-Stilbene and *cis*-Azobenzene Photoisomerization

Amanda J. Neukirch, Logan C. Shamberger, Enrique Abad, Barry J. Haycock, Hong Wang, José Ortega, Oleg V. Prezhdo, James P. Lewis [West Virginia University]

J. Chem. Theor. and Comp., **10**, 14–23, 2014.

Structurally, stilbene and azobenzene molecules exist in closed and open *cis* and *trans* forms, which are able to transform into each other under the influence of light (photoisomerization). We have successfully implemented nonadiabatic couplings and a surface-hopping algorithm within a density functional theory approach that utilizes local orbitals. We demonstrate the effectiveness of our approach by performing molecular dynamics simulations of the *cis*–*trans* photoisomerization in both azobenzene and stilbene upon excitation into the S₁ state.

Isotropic Periodic Sum Treatment of Long-Range Electrostatic Interactions in Combined Quantum Mechanical and Molecular Mechanical Calculations

Pedro Ojeda-May, Jingzhi Pu [Indiana University-Purdue University Indianapolis]

J. Chem. Theor. and Comp., **10**, 134–145, 2014.

The isotropic periodic sum (IPS) method was extended to describe long-range electrostatic interactions in combined quantum mechanical and molecular mechanical (QM/MM) calculations. The resulting method, designated QM/MM-IPS, was tested for two ion association processes and a model S_N2 reaction in aqueous solution. Potential of mean force (PMF) profiles and radial distribution functions computed from the QM/MM-IPS simulations were compared with those obtained by using the existing QM/MM-Ewald sum and cutoff (QM/MM-Cutoff) methods.

QM and QM/MM (Cont'd)

Generalized QM/MM Force Matching Approach Applied to the 11-cis Protonated Schiff Base Chromophore of Rhodopsin

Manuel Doemer, Patrick Maurer, Pablo Campomanes, Ivano Tavernelli, Ursula Rothlisberger [Ecole Polytechnique Fédérale de Lausanne]

J. Chem. Theor. and Comp., **10**, 412–422, 2014.

We extended a previously developed force matching approach to systems with covalent QM/MM boundaries and describe its user-friendly implementation in the publicly available software package CPMD. We applied this approach to the challenging case of the retinal protonated Schiff base in dark state bovine rhodopsin. We were able to develop a highly accurate force field that is able to capture subtle structural changes within the chromophore that have a pronounced influence on the optical properties.

FT-IR Spectroscopy and Density Functional Theory Calculations of ^{13}C Isotopologues of the Helical Peptide Z-Aib₆-OtBu

Timothy Zeko, Steven F. Hannigan, Timothy Jacisin, Matthew J. Guberman-Pfeffer, Eric R. Falcone, Melissa J. Guildford, Christopher Szabo, Kathryn E. Cole, Jessica Placido, Erin Daly, Matthew A. Kubasik [Fairfield University]

J. Phys. Chem. B., **118**, 58–68, 2014.

Isotope-edited FT-IR spectroscopy is a combined synthetic and spectroscopic method used to characterize local (e.g., residue-level) vibrational environments of biomolecules. We have prepared the 3₁₀ helical peptide Z-Aib₆-OtBu and seven ^{13}C -enriched analogues that vary only in the number and position(s) of $^{13}\text{C}=\text{O}$ isotopic enrichment. FT-IR spectra of these eight peptides solvated in the nonpolar aprotic solvent dichloromethane have been collected and compared to frequency, intensity, and normal mode results of DFT calculations.

Comparative or Homology Modeling

Applying Molecular Crowding Models to Simulations of Virus Capsid Assembly *In Vitro*

Gregory R. Smith, Lu Xie, Byoungkoo Lee, Russell Schwartz [Carnegie Mellon University]

Biophysical Journal. **106**, 310-320, 2014.

A!

Virus capsid assembly has been widely studied as a biophysical system, both for its biological and medical significance and as an important model for complex self-assembly processes. Here, we explore one specific feature characteristic of the intracellular environment and known to have large effects on macromolecular assembly processes: molecular crowding. We combine prior particle simulation methods for estimating crowding effects with coarse-grained stochastic models of capsid assembly, using the crowding models to adjust kinetics of capsid simulations to examine possible effects of crowding on assembly pathways.

Homology modeling of *T. cruzi* and *L. major* NADH-dependent fumarate reductases: Ligand docking, molecular dynamics validation, and insights on their binding modes

Alicia Merlino, Marisol Vieites, Dinorah Gambino, E. Laura Coitiño [Universidad de la República]

J. Mol. Graph. and Mod., **48**, 47-59, 2014.

Leishmania major and *Trypanosoma cruzi* are the main causes of leishmaniasis and Chagas disease, two endemic parasitosis identified as neglected diseases by the World Health Organization. Fumarate reductase (FR) is a central enzyme in the conversion of fumarate to succinate, an energy releasing path essential for the survival of these protozoans which is also absent in their mammalian hosts. Here we used homology modeling combined with enzyme-cofactor docking to propose tertiary structures for NADH-dependent LmFR and TcFR using an homologous X-ray crystallographic structure of flavin-adenine dinucleotide (FAD) dependent FR from *Shewanella frigidimarina* as template.

Comparative and Homology Modeling (Cont'd)

A structure-guided approach for protein pocket modeling and affinity prediction

Rocco Varela, Ann E. Cleves, Russell Spitzer, Ajay N. Jain
[University of California]

J. Comp. Aided. Mol. Design, **27**, 917-934, 2014.

We introduce a method to integrate protein structure information into the model induction process in order to construct more robust physical models. The structure-guided models accurately predict binding affinities over a broad range of compounds while producing more accurate representations of the protein pockets and ligand binding modes. Structure-guidance for the QMOD method yielded significant performance improvements, both for affinity and pose prediction, especially in cases where predictions were made on ligands very different from those used for model induction.

Partitioning of Amino Acids into a Model Membrane: Capturing the Interface

Taras V. Pogorelov, Josh V. Vermaas, Mark J. Arcario, Emad Tajkhorshid [University of Illinois at Urbana-Champaign]

J. Phys. Chem. B., **118**, 1481–1492, 2014.

A!

Energetics of protein side chain partitioning between aqueous solution and cellular membranes is of fundamental importance for correctly capturing the membrane binding and specific protein–lipid interactions of peripheral membrane proteins. We recently reported a highly mobile membrane mimetic (HMMM) model that accelerates lipid dynamics by modeling the membrane interior partially as a fluid organic solvent while retaining a literal description of the lipid head groups and the beginning of the tails. We report here the free energy profiles for partitioning of 10 protein side chain analogues into a HMMM membrane.

Ligand Docking

Coarse-Grained Simulations of the HIV-1 Matrix Protein Anchoring: Revisiting Its Assembly on Membrane Domains

Landry Charlier, Maxime Louet, Laurent Chaloin, Patrick Fuchs, Jean Martinez, Delphine Muriaux, Cyril Favard, Nicolas Floquet [Université Montpellier 1]

Biophysical Journal. **106**, 577-585, 2014.

In the accepted model for human immunodeficiency virus preassembly in infected host cells, the anchoring to the intracellular leaflet of the membrane of the matrix domain (MA) that lies at the N-terminus of the viral Gag protein precursor appears to be one of the crucial steps for particle assembly. In this study, we simulated the membrane anchoring of human immunodeficiency virus-1 myristoylated MA protein using a coarse-grained representation of both the protein and the membrane.

Molecular dynamics simulations show how the FMRP Ile304Asn mutation destabilizes the KH2 domain structure and affects its function

Daniele Di Marino, Tilmann Achsel, Caroline Lacoux, Mattia Falconi, Claudia Bagni [Catholic University of Leuven]

J. Biomol. Stru. and Dyn., **32**, 337-350, 2014.

Mutations or deletions of FMRP, involved in the regulation of mRNA metabolism in brain, lead to the Fragile X syndrome (FXS), the most frequent form of inherited intellectual disability. A severe manifestation of the disease has been associated with the Ile304Asn mutation, located on the KH2 domain of the protein. Several hypotheses have been proposed to explain the possible molecular mechanism responsible for the drastic effect of this mutation in humans. Here, we performed a molecular dynamics simulation and show that the Ile304Asn mutation destabilizes the hydrophobic core producing a partial unfolding of two α -helices and a displacement of a third one.

Ligand Docking (Cont'd)

Relationship between a point mutation S97C in CK1δ protein and its affect on ATP-binding affinity

Ambuj Kumar, Vidya Rajendran, Rao Sethumadhavan ,
Rituraj Purohit[Vellore Institute of Technology University]

J. Biomol. Stru. and Dyn., **32**, 394-405, 2014.

CK1δ (Casein kinase I isoform delta) is a member of CK1 kinase family protein that mediates neurite outgrowth and the function as brain-specific microtubule-associated protein. ATP binding kinase domain of CK1δ is essential for regulating several key cell cycle signal transduction pathways. Mutation in CK1δ protein is reported to cause cancers and affects normal brain development. S97C mutation in kinase domain of CK1δ protein has been involved to induce breast cancer and ductal carcinoma. We performed molecular docking studies to examine the effect of this mutation on its ATP-binding affinity.

Investigation on the mechanism for the binding and drug resistance of wild type and mutations of G86 residue in HIV-1 protease complexed with Darunavir by molecular dynamic simulation and free energy calculation

Dan Li, Ying Zhang, Run-Ning Zhao, Song Fan, Ju-Guang Han [University of Science and Technology of China]

J. Mol.Mod., **20**, 20:2122, 2014.

Residue Gly86 is considered as the highly conserved residue in the HIV-1 protease. In our work, the detailed binding free energies for the wild-type (WT) and mutated proteases binding to the TMC-114 are estimated to investigate the protein-inhibitor binding and drug resistance mechanism by molecule dynamic simulations and molecular mechanics Poisson Boltzmann surface area (MM-PBSA) method. The binding affinities between the mutants and inhibitor are different than that in the wild-type complex and the major resistance to Darunavir (DRV) of G86A and G86S originate from the electrostatic energy and entropy, respectively.

Classifier Ensemble Based on Feature Selection and Diversity Measures for Predicting the Affinity of A_{2B} Adenosine Receptor Antagonists

Isis Bonet, Pedro Franco-Montero, Virginia Rivero, Marta Teijeira, Fernanda Borges, Eugenio Uriarte, Aliuska Morales Helguera [Universidade do Porto]

J.Chem. Infor. and Mod. **53**, 3140–3155, 2014.

A_{2B} adenosine receptor antagonists may be beneficial in treating diseases like asthma, diabetes, diabetic retinopathy, and certain cancers. This has stimulated research for the development of potent ligands for this subtype, based on quantitative structure-affinity relationships. In this work, a new ensemble machine learning algorithm is proposed for classification and prediction of the ligand-binding affinity of A_{2B} adenosine receptor antagonists. This algorithm is based on the training of different classifier models with multiple training sets (composed of the same compounds but represented by diverse features). The *k*-nearest neighbor, decision trees, neural networks, and support vector machines were used as single classifiers.

New Strategy for Receptor-Based Pharmacophore Query Construction: A Case Study for 5-HT₇ Receptor Ligands

Rafał Kurczab , Andrzej J. Bojarski [Institute of Pharmacology Polish Academy of Sciences]

J.Chem. Infor. and Mod. **53**, 3233–3243, 2014.

A!

In this paper, a new approach for generating receptor-based 3D pharmacophore models for rapid *in silico* virtual screening is presented. The method combines information from docking poses of known ligands of different structures and further ligand–receptor complexes analyses using structural interaction fingerprints (SIFts). Next, the best linear combination of three-, four-, and five-feature pharmacophores in terms of selected performance parameter (i.e., recall, F-score, and MCC) is constructed.

Ligand Docking (Cont'd)

Inclusion of Multiple Fragment Types in the Site Identification by Ligand Competitive Saturation (SILCS) Approach

E. Prabhu Raman, Wenbo Yu, Sirish K. Lakkaraju, Alexander D. MacKerell, Jr.

J.Chem. Infor. and Mod. **53**, 3384–3398, 2014.

The site identification by ligand competitive saturation (SILCS) method identifies the location and approximate affinities of small molecular fragments on a target macromolecular surface by performing molecular dynamics (MD) simulations of the target in an aqueous solution of small molecules representative of different chemical functional groups. In this study, we introduce a set of small molecules to map potential interactions made by neutral hydrogen bond donors and acceptors and charged donor and acceptor fragments in addition to nonpolar fragments.

Bridging Molecular Docking to Membrane Molecular Dynamics To Investigate GPCR–Ligand Recognition: The Human A_{2A} Adenosine Receptor as a Key Study

Davide Sabbadin, Antonella Ciancetta, Stefano Moro [Università di Padova]

J.Chem. Infor. and Mod. **54**, 169–183, 2014.

A!

G protein-coupled receptors (GPCRs) represent the largest family of cell-surface receptors and about one-third of the actual targets of clinically used drugs. In the present work, we present a novel approach consisting in the integration of molecular docking and membrane MD simulations with the aim to merge the rapid sampling of ligand poses into the binding site, typical of docking algorithms, with the thermodynamic accuracy of MD simulations in describing, at the molecular level, the stability a GPCR-ligand complex embedded into explicit lipid–water environment.

Ligand and Structure-Based Classification Models for Prediction of P-Glycoprotein Inhibitors

Freya Klepsch, Poongavanam Vasanthanathan, Gerhard F. Ecker [University of Vienna]

J.Chem. Infor. and Mod. **54**, 218–229, 2014.

The ABC transporter P-glycoprotein (P-gp) actively transports a wide range of drugs and toxins out of cells, and is therefore related to multidrug resistance and the ADME profile of therapeutics. The present study aims at comparing the P-gp inhibitor/noninhibitor classification performance obtained by docking into a homology model of P-gp, to supervised machine learning methods, such as Kappa nearest neighbor, support vector machine (SVM), random forest and binary QSAR, by using a large, structurally diverse data set.

Identification and Characterization of Noncovalent Interactions That Drive Binding and Specificity in DD-Peptidases and β -Lactamases

Jacqueline C. Hargis, Sai Lakshmana Vankayala, Justin K. White, H. Lee Woodcock [University of South Florida]

J. Chem. Theor. and Comp. **10**, 855–864, 2014.

Bacterial resistance to standard (i.e., β -lactam-based) antibiotics has become a global pandemic. Simultaneously, research into the underlying causes of resistance has slowed substantially, although its importance is universally recognized. Key to unraveling critical details is characterization of the noncovalent interactions that govern binding and specificity (DD-peptidases, antibiotic targets, versus β -lactamases, the evolutionarily derived enzymes that play a major role in resistance) and ultimately resistance as a whole. Herein, we describe a detailed investigation that elicits new chemical insights into these underlying intermolecular interactions.

Ligand Docking (Cont'd)

Ligand Uptake Modulation by Internal Water Molecules and Hydrophobic Cavities in Hemoglobins

Juan P. Bustamante, Stefania Abbruzzetti, Agnese Marcelli, Diego Gauto, Leonardo Boechi, Alessandra Bonamore, Alberto Boffi, Stefano Bruno, Alessandro Feis, Paolo Foggi, Dario A. Estrin, Cristiano Viappiani [University of Parma]

J. Phys. Chem. B., **118**, 1234–1245, 2014.

Internal water molecules play an active role in ligand uptake regulation, since displacement of retained water molecules from protein surfaces or cavities by incoming ligands can promote favorable or disfavorable effects over the global binding process. Detection of these water molecules by X-ray crystallography is difficult given their positional disorder and low occupancy. In this work, we employ a combination of molecular dynamics simulations and ligand rebinding over a broad time range to shed light into the role of water molecules in ligand migration and binding.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 48, January 2014.

- 1-8 **Modeling the intermolecular interactions: Molecular structure of N-3-hydroxyphenyl-4-methoxybenzamide** Sedat Karabulut [Balıkesir University], Hilmi Namli, Raif Kurtaran, Leyla Tatar Yildirim, Jerzy Leszczynski

The title compound, N-3-hydroxyphenyl-4-methoxybenzamide (**3**) was prepared by the acylation reaction of 3-aminophenol (**1**) and 4-methoxybenzoylchloride (**2**) in THF and characterized by ^1H NMR, ^{13}C NMR and elemental analysis. Molecular structure of the crystal was determined by single crystal X-ray diffraction and DFT calculations.

- 9-17 **Theoretical study of the geometries and decomposition energies of CO_2 on Al_{12}X : Doping effect of Al_{12}X** Jian-Ying Zhao, Feng-Qi Zhao, Si-Yu Xu, Xue-Hai Ju [Nanjing University of Science and Technology]

The adsorption and decomposition of CO_2 molecule on X-centered icosahedral Al_{12}X clusters (doping atom X = Al, Be, Zn, Fe, Ni, Cu, B, C, Si, P) were investigated by the DFT methods of PW91 and PWC.

- 18-27 **Mechanism and kinetic study of 3-fluoropropene with hydroxyl radical reaction** Yunju Zhang, Kai Chao, Xiumei Pan, Jingping Zhang, Zhongmin Su, Rongshun Wang [Northeast Normal University]

Potential energy surface for the reaction of hydroxyl radical (OH) with 3-fluoropropene ($\text{CH}_2=\text{CHCH}_2\text{F}$) has been studied to evaluate the reaction mechanisms, possible products and rate constants. It has been shown that the $\text{CH}_2=\text{CHCH}_2\text{F}$ with OH reaction takes place via a barrierless addition/elimination and hydrogen abstraction mechanism.

- 28-35 **Enhancement of second-order nonlinear optical response in boron nitride nanocone: Li-doped effect** Wen-Yong Wang, Na-Na Ma, Cun-Huan Wang, Meng-Ying Zhang, Shi-Ling Sun, Yong-Qing Qiu [Northeast Normal University]

The unusual properties of Li-doped boron nitride nanomaterials have been paid further attention due to their wide applications in many promising fields. Here, density functional theory (DFT) calculations have been carried out to investigate the second-order nonlinear optical (NLO) properties of boron nitride nanocone (BNNC) and its Li-doped BNNC derivatives

- 36-46 **Insight into the structural mechanism for PKB α allosteric inhibition by molecular dynamics simulations and free energy calculations** Shi-Feng Chen, Yang Cao, Shuang Han, Jian-Zhong Chen [Zhejiang University]

See Applications / Ligand Binding.

- 47-59 **Homology modeling of T. cruzi and L. major NADH-dependent fumarate reductases: Ligand docking, molecular dynamics validation, and insights on their binding modes** Alicia Merlino, Marisol Vieites, Dinorah Gambino, E. Laura Coitiño [Universidad de la República]

See Methodology / Homology Modeling.

- 60-69 **Mechanism, kinetics and atmospheric fate of $\text{CF}_3\text{CH}=\text{CH}_2$, $\text{CF}_3\text{CF}=\text{CH}_2$, and $\text{CF}_3\text{CF}=\text{CF}_2$ by its reaction with OH-radicals: CVT/SCT/ISPE and hybrid meta-DFT methods**Balaganesh M., Rajakumar B. [Indian Institute of Technology Madras]

The dual level direct dynamic study is carried out for the reactions of $\text{CF}_3\text{CH}=\text{CH}_2$, $\text{CF}_3\text{CF}=\text{CH}_2$ and $\text{CF}_3\text{CF}=\text{CF}_2$ with hydroxyl radicals. The dynamic calculations are performed using the variational transition state theory (VTST) with interpolated single-point energies (ISPE) method at M06-2X/MG3S//M06-2X/6-31+G(d,p) level of theory.

- 70-79 **Multivariate SAR and QSAR of cucurbitacin derivatives as cytotoxic compounds in a human lung adenocarcinoma cell line**Karen L. Lang, Izabella T. Silva, Vanessa R. Machado, Lara A. Zimmermann, Miguel S.B. Caro, Cláudia M.O. Simões, Eloir P. Schenkel, Fernando J. Durán, Lílían S.C. Bernardes, Eduardo B. de Melo [Western Paraná State University (Unioeste)]

See Applications / QSAR.

- 80-86 **MDWiZ: A platform for the automated translation of molecular dynamics simulations**vVictor H. Rusu, Vitor A.C. Horta, Bruno A.C. Horta, Roberto D. Lins, Riccardo Baron [The University of Utah]

See Applications / Bioinformatics.

- 87-95 **Models for H_3 receptorz antagonist activity of sulfonylurea derivatives** Naveen Khatri , A.K. Madan [Pt. B. D. Sharma University of Health Sciences]

The histamine H_3 receptor has been perceived as an auspicious target for the treatment of various central and peripheral nervous system diseases. In present study, a wide variety of 60 2D and 3D molecular descriptors (MDs) were successfully utilized for the development of models for the prediction of antagonist activity of sulfonylurea derivatives for histamine H_3 receptors.

- 96-104 **Small molecule interaction with lipid bilayers: A molecular dynamics study of chlorhexidine**Brad Van Oosten [Brock University], Drew Marquardt, Ivana Komljenović, Jeremy P. Bradshaw, Edward Sternin, Thad A. Harroun

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 105-117 **Antileishmanial phytochemical phenolics: Molecular docking to potential protein targets** Ifedayo Victor Ogunbe [Jackson State University], William R. Erwin, William N. Setzer

See Applications / Medicinal Chemmistry and Drug Design.

Journal of Molecular Graphics and Modelling, 49, February 2014.

- 1-10 **Quantum mechanical investigations on the role of C-terminal residue in influencing the structural features of dipeptides containing N-terminal proline** Gunajyoti Das, Shilpi Mandal [North Eastern Hill University]

See Methodology / QM and QM/MM.

- 11-17 **Fletcher-Reeves based Particle Swarm Optimization for prediction of molecular structure** Shikha Agrawal [University Institute of Technology, Rajiv Gandhi Proudhyogiki Vishwavidhyalaya], Sanjay Silakari

The determination of the most stable conformers of a molecule can be formulated as a global optimization problem. In this paper, we propose a hybrid approach combining Particle Swarm Optimization (PSO) and the Fletcher-Reeves algorithm to minimize the potential energy function.

- 18-24 **Identification of p38 α MAP kinase inhibitors by pharmacophore based virtual screening** Rahul P. Gangwal, Nihar R. Das, Kaushik Thanki, Mangesh V. Damre, Gaurao V. Dhoke, Shyam S. Sharma, Sanyog Jain, Abhay T. Sangamwar [National Institute of Pharmaceutical Education and Research (NIPER)]

See Applications / Medicinal Chemistry and Drug Design.

- 25-37 **Discovery of potent inhibitor for matrix metalloproteinase-9 by pharmacophore based modeling and dynamics simulation studies** Suresh Kalva, E.R. Azhagiya Singam, V. Rajapandian, Lilly M. Saleena [SRM University], V. Subramanian

See Applications / Medicinal Chemistry and Drug Design.

Journal of Computational Chemistry, 35(2), January 2014.

- 95-108 **An extensible interface for QM/MM molecular dynamics simulations with AMBER**, Andreas W. Götz [University of California San Diego], Matthew A. Clark and Ross C. Walker

See Methodology / QM and QM/MM.

- 109-120 **The photoisomerization of 11-cis-retinal protonated Schiff base in gas phase: Insight from spin-flip density functional theory**, Panwang Zhou, Jianyong Liu, Keli Han and Guozhong He

This extensive theoretical study employed the spin-flip density functional theory (SFDFT) method to investigate the photoisomerization of 11-cis-retinal protonated Schiff base (PSB11) and its minimal model *t*Zt-penta-3,5-dieniminium cation (PSB3). Our calculated results indicate that SFDFT can perform very well in describing the ground- and excited-state geometries of PSB3 and PSB11.

- 121–129 **A new size extensive multireference perturbation theory** ,Feiwu Chen [University of Science and Technology Beijing,] and Zhihui Fan

A new multireference perturbation series is derived based on the Rayleigh–Schrödinger perturbation theory. It is orbitally invariant. Its computational cost is comparable to the single reference Møller–Plesset perturbation theory.

- 130–149 **Calibration of forcefields for molecular simulation: Sequential design of computer experiments for building cost-efficient kriging metamodels** ,Fabien Cailliez [Univ. Paris-Sud and CNR], Arnaud Bourasseau,Pascal Pernot

See Methodology / Potentials and Parameters.

- 150–158 **Hamiltonian replica-exchange simulations with adaptive biasing of peptide backbone and side chain dihedral angles** ,Katja Ostermeir, Martin Zacharias [Technische Universität München]

See Applications / Protein Conformational Analysis.

- 159–165 **Study of $\text{Cl}^-(\text{H}_2\text{O})_n$ ($n = 1-4$) using basin-hopping method coupled with density functional theory** ,Shuai Jiang, Yi-Rong Liu, Teng Huang, Hui Wen, Kang-Ming Xu, Wei-Xiong Zhao, Wei-Jun Zhang and Wei Huang [University of Science and Technology of China]

$\text{Cl}^-(\text{H}_2\text{O})_n$ ($n = 1-4$) clusters were investigated using a basin-hopping (BH) algorithm coupled with density functional theory (DFT). Structures, energetics, thermodynamics, vertical detachment energies, and vibrational frequencies were obtained from high-level *ab initio* calculations.

- 166–173 **Exploring transition state structures for intramolecular pathways by the artificial force induced reaction method** ,Satoshi Maeda [Hokkaido University], Tetsuya Taketsugu and Keiji Morokuma

Finding all required transition state (TS) structures is an important but hard task in theoretical study of complex reaction mechanisms. In the present article, an efficient automated TS search method, artificial force induced reaction (AFIR), was extended to intramolecular reactions.

- 174–180 **Multiscale simulation of pollution gases adsorption in porous organic cage CC3** ,Wenliang Li and Jingping Zhang [Northeast Normal University]

A general multiscale simulation procedure is proposed to accurately predict the uptakes of pollution gases such as CO_2 , SO_2 , H_2S , and CO in one of the most investigated porous organic cages CC3 by using a sophisticated force field vdW3 fitted by double hybrid functional (B2PLYP) with a dispersion correction (D3) separately for gas–gas and CC3–gas interactions.

Journal of Computational Chemistry, 35 (3), January 2014.

- 181–191 **Accurate density functional theory description of binding constants and NMR chemical shifts of weakly interacting complexes of C₆₀ with corannulene-based molecular bowls** Ivan Welsh and Matthias Lein [Victoria University of Wellington]

Density functional calculations on “catch and release” complexes of C₆₀ with corannulene derived molecular bowls show that computationally obtained ¹H nuclear magnetic resonance (NMR) chemical shifts can be used as a reliable predictor of binding constants. A wide range of functionals was benchmarked against accurate *ab initio* calculations to ensure a credible representation of the weak forces that dominate the interactions in these systems.

- 192–198 **Assessing protein–ligand docking for the binding of organometallic compounds to proteins,** Elisabeth Ortega-Carrasco, Agusti Lledós and Jean-Didier Maréchal [Universitat Autònoma de Barcelona]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 199–203 **Basis sets for the evaluation of van der Waals complex interaction energies: Ne–N₂ intermolecular potential and microwave spectrum** ,Angelika Baranowska-Lączkowska and Berta Fernández [University of Santiago de Compostela]

In order to obtain efficient basis sets for the evaluation of van der Waals complex intermolecular potentials, we carry out systematic basis set studies. For this, interaction energies at representative geometries on the potential energy surfaces are evaluated using the CCSD(T) correlation method and large polarized LPol-n and augmented polarization-consistent aug-pc-2 basis sets extended with different sets of midbond functions.

- 204–213 **Adsorption of multivalent alkylthiols on Au(111) surface: Insights from DFT**
Edoardo Fertitta [Freie Universität Berlin], Elena Voloshina and Beate Paulus

The adsorption of multivalent thiols on gold (111) surface was investigated using density functional theory applying the Perdew–Burke–Ernzerhof functional.

- 214–226 **Quantitative structure–property relationship modeling of Grätzel solar cell dyes** ,Vishwesh Venkatraman, Per-Olof Åstrand and Bjørn Kåre Alsberg [Norwegian University of Science and Technology]

With fossil fuel reserves on the decline, there is increasing focus on the design and development of low-cost organic photovoltaic devices, in particular, dye-sensitized solar cells (DSSCs). The power conversion efficiency (PCE) of a DSSC is heavily influenced by the chemical structure of the dye.

- 227–243 **Net charge changes in the calculation of relative ligand-binding free energies via classical atomistic molecular dynamics simulation** ,Maria M. Reif and Chris Oostenbrink [University of Natural Resources and Life Sciences Vienna]

See Application / Free Energy Calculations.

- 244–259 **Atomistic kinetic Monte Carlo study of atomic layer deposition derived from density functional theory** ,Mahdi Shirazi and Simon D. Elliott [University College Cork]

To describe the atomic layer deposition (ALD) reactions of HfO_2 from $\text{Hf}(\text{N}(\text{CH}_3)_2)_4$ and H_2O , a three-dimensional on-lattice kinetic Monte-Carlo model is developed. In this model, all atomistic reaction pathways in density functional theory (DFT) are implemented as reaction events on the lattice.

- 260–269 **An efficient and extensible format, library, and API for binary trajectory data from molecular simulations** ,Magnus Lundborg, Rossen Apostolov, Daniel Spångberg, Anders Gärdenäs, David van der Spoel and Erik Lindahl [Stockholm University]

See Applications / Bioinformatics.

Journal of Computational Chemistry, 35(4), February 2014.

- 271–274 **Why is $\text{N}\cdots\text{Be}$ distance of $\text{NH}_3\text{H}^+\cdots\text{DBeH}$ shorter than that of $\text{NH}_3\text{D}^+\cdots\text{HBeH}$? paradoxical geometrical isotope effects for partially isotope-substituted dihydrogen-bonded isotopomers** ,Taro Udagawa [Gifu University] , Masanori Tachikawa

The partial isotope substitution for the change of geometrical parameters, interaction energies, and nuclear magnetic shielding tensors (σ) of dihydrogen-bonded $\text{NH}_3\text{X}^+\cdots\text{YBeH}$ (X, Y = H, D, and T) systems is analyzed.

- 275–289 **Highly asymmetric electrolytes in the primitive model: Hypernetted chain solution in arbitrary spatial dimensions** ,Marco Heinen [Heinrich-Heine-Universität], Elshad Allahyarov , Hartmut Löwen

The pair-correlation functions for fluid ionic mixtures in arbitrary spatial dimensions are computed in hypernetted chain (HNC) approximation. In the primitive model (PM), all ions are approximated as nonoverlapping hyperspheres with Coulomb interactions.

- 290–299 **Algorithms for computer detection of symmetry elements in molecular systems** ,Otávio Beruski , Luciano N. Vidal [Federal University of Technology – Paraná]

Simple procedures for the location of proper and improper rotations and reflexion planes are presented. The search is performed with a molecule divided into subsets of symmetrically equivalent atoms (SEA) which are analyzed separately as if they were a single molecule.

- 300–308 **Multidimensional umbrella sampling and replica-exchange molecular dynamics simulations for structure prediction of transmembrane helix dimers** ,Pai-Chi Li, Naoyuki Miyashita, Wonpil Im, Satoshi Ishido and Yuji Sugita [RIKEN Theoretical Molecular Science Laboratory]

See Applications / Protein Structure Analysis.

- 309–312 **Are accurate computations of the $^{13}\text{C}'$ shielding feasible at the DFT level of theory?** ,Jorge A. Vila [Universidad Nacional de San Luis], Yelena A. Arnautova, Osvaldo A. Martin and Harold A. Scheraga

The goal of this study is twofold. First, to investigate the relative influence of the main structural factors affecting the computation of the $^{13}\text{C}'$ shielding, namely, the conformation of the residue itself and the next nearest-neighbor effects. Second, to determine whether calculation of the $^{13}\text{C}'$ shielding at the density functional level of theory (DFT), with an accuracy similar to that of the $^{13}\text{C}^{\alpha}$ shielding, is feasible with the existing computational resources.

- 313–323 **Multireference space without first solving the configuration interaction problem** , Vitaly N. Glushkov [Oles Gonchar Dnipropetrovsk National University] , Xavier Assfeld

We further develop an idea to generate a compact multireference space without first solving the configuration interaction problem previously proposed for the ground state (GS) (Glushkov, Chem. Phys. Lett. 1995, 244, 1).

- 324–334 **A combined semiempirical and DFT computational protocol for studying bioorganometallic complexes: Application to molybdocene–cysteine complexes** , Dimas Suárez [Universidad de Oviedo], Natalia Díaz and Ramón López

See Methodology / QM and QM/MM.

- 335–341 **LEAP: Highly accurate prediction of protein loop conformations by integrating coarse-grained sampling and optimized energy scores with all-atom refinement of backbone and side chains** , Shide Liang, Chi Zhang and Yaoqi Zhou [Griffith University]

See Applications / Protein Conformational Analysis.

Journal of Computational Chemistry, 35 (5), February 2014.

- 343–359 **Multipolar electrostatics for proteins: Atom–atom electrostatic energies in crambin** , Yongna Yuan, Matthew J. L. Mills and Paul L. A. Popelier [University of Manchester]

See Methodology / QM and QM/MM.

- 360–370 **Development and use of an atomistic CHARMM-based forcefield for peptoid simulation** , Dina T. Mirijanian, Ranjan V. Mannige, Ronald N. Zuckermann and Stephen Whitelam [Lawrence Berkeley National Laboratory]

See Methodology / Potentials and Parameters.

- 371–376 **Origin of the “endo rule” in Diels–Alder reactions** , Israel Fernández [Universidad Complutense de Madrid] , F. Matthias Bickelhaupt

Detailed density functional theory calculations definitively rationalize the preference for the endo cycloadduct (also known as endo rule) in text-book thermal Diels–Alder reactions involving maleic anhydride and cyclopentadiene or butadiene.

- 377–385 **Comparing distance metrics for rotation using the k -nearest neighbors algorithm for entropy estimation** ,David J. Huggins [University of Cambridge]

Distance metrics facilitate a number of methods for statistical analysis. For statistical mechanical applications, it is useful to be able to compute the distance between two different orientations of a molecule. However, a number of distance metrics for rotation have been employed, and in this study, we consider different distance metrics and their utility in entropy estimation using the k -nearest neighbors(KNN) algorithm.

- 386–394 **Halogen bonds with benzene: An assessment of DFT functionals** ,Alessandra Forni, Stefano Pieraccini, Stefano Rendine , Maurizio Sironi [Università degli Studi di Milano]

The performance of an extensive set of density functional theory functionals has been tested against CCSD(T) and MP2 results, extrapolated to the complete basis set (CBS) limit, for the interaction of either DCI or DBr ($D = H, HCC, F, \text{ and } NC$) with the aromatic system of benzene.

- 395–405 **TiS₂ and ZrS₂ single- and double-wall nanotubes: First-principles study** ,Andrei V. Bandura [St. Petersburg State University] , Robert A. Evarestov

Hybrid density functional theory has been applied for investigations of the electronic and atomic structure of bulk phases, nanolayers, and nanotubes based on titanium and zirconium disulfides. Calculations have been performed on the basis of the localized atomic functions by means of the CRYSTAL-2009 computer code.

- 406–413 **New faster CHARMM molecular dynamics engine** ,Antti-Pekka Hynninen [National Renewable Energy Laboratory], Michael F. Crowley

See Applications / Bioinformatics.

Journal of Molecular Modeling, 20 (1), January 2014.

- 2080 **Discovery of novel urokinase plasminogen activator (uPA) inhibitors using ligand-based modeling and virtual screening followed by in vitro analysis** ,Mahmoud A. Al-Sha'er, Mohammad A. Khanfar, Mutasem O. Taha [University of Jordan]

See Applications / Enzyme Catalysis.

- 2079 **Density functional studies of the stepwise substitution of pyridine, pyridazine, pyrimidine, pyrazine, and 1,3,5-triazine with BCO** ,Xiao-Fang Qin [Ludong University], Feng Wang, Hai-Shun Wu

The structures, stabilities, and aromaticities of a series of $(BCO)_n(CH)_{5-n}N$ ($n = 0-5$), $(BCO)_n(CH)_{4-n}N_2$ ($n = 0-4$), and $1,3,5-(BCO)_n(CH)_{3-n}N_3$ ($n = 0-3$) clusters were investigated at the B3LYP density functional level of theory. The most stable positional isomers of individual clusters were obtained. All of the calculated CO binding energies were positive, suggesting that the BCO-substituted species are stable.

- 2077 **Quantitative characterization of protein tertiary motifs** ,Rajani R. Joshi [IIT Bombay], S. Sreenath

See Applications / Protein Structure Analysis.

- 2076 **Theoretical study of $X^- \cdot 1 \cdot YF$ (1 = triazine, X = Cl, Br and I, Y = H, Cl, Br, I, PH_2 and AsH_2): noncovalently electron-withdrawing effects on anion-arene interactions** ,Yishan Chen [Qujing Normal University], Lifeng Yao

The ternary complexes $X^- \cdot 1 \cdot YF$ (1 = triazine, X = Cl, Br and I, Y = H, Cl, Br, I, PH_2 and AsH_2) have been investigated by MP2 calculations to understand the noncovalently electron-withdrawing effects on anion-arene interactions. The results indicate that in binary complexes ($1 \cdot X^-$), both weak σ -type and anion- π complexes can be formed for Cl^- and Br^- , but only anion- π complex can be formed for I^- .

- 2073 **Density functional investigations on 2-naphthalenecarbonitrile dimerization within cucurbit[8]uril cavitand** ,Swarada R. Peerannawar, Soniya S. Rao, Shridhar P. Gejji [University of Pune]

Dimerization of 2-naphthalenecarbonitrile (2-NpCN) mediated by cucurbit[8]uril (CB[8]) has been investigated employing the density functional theory.

- 2072 **First-principles study of electric field effects on the structure, decomposition mechanism, and stability of crystalline lead styphnate** ,Zhimin Li, Huisheng Huang, Tonglai Zhang [Beijing Institute of Technology], Shengtao Zhang, Jianguo Zhang, Li Yang

The electric field effects on the structure, decomposition mechanism, and stability of crystalline lead styphnate have been studied using density functional theory. The results indicate that the influence of external electric field on the crystal structure is anisotropic.

- 2071 **DFT study of ozone dissociation on BC_3 graphene with Stone–Wales defects** ,Ali Ahmadi Peyghan, Morteza Moradi [Materials and Energy Research Center, Karaj]

Ozone (O_3) adsorption on pristine Stone–Wales (SW) defective BC_3 graphene-like sheets was investigated using density functional calculations. It was found that O_3 is weakly adsorbed on the pristine sheet. Two types of SW-defective sheets were studied, SW-CC and SW-BC, in which a defect is formed by rotating a C–C or B–N bond, respectively.

- 2069 **How “drug-like” are naturally occurring anti-cancer compounds?** ,Fidele Ntie-Kang [University of Buea], Lydia L. Lifongo, Philip N. Judson, Wolfgang Sippl, Simon M. N. Efange

We attempt to evaluate the “drug-likeness” of a collection of ~1500 natural products, exhibiting in vitro or in vivo activities against cancers of various forms, by using a set of calculated molecular descriptors. Compliance to Lipinski’s “Rule of Five” and Jorgensen’s “Rule of Three” have been used to assess oral availability, by making use of popular parameters like molecular weights, predicted lipophilicities, number of hydrogen bond donors/acceptors, predicted aqueous solubilities, number of primary metabolites and Caco-2 permeabilities.

Journal of Molecular Modeling, 20 (2), February 2014.

- 2136 **C-H... π interactions in proteins: prevalence, pattern of occurrence, residue propensities, location, and contribution to protein stability**, Manjeet Kumar, Petety V. Balaji [Indian Institute of Technology Bombay]

See Methodology / Molecular Dynamics.

- 2126 **Solvent effects on polarizability and hyperpolarizability of spirobifluorene derivative**, Hai-Peng Li [China University of Mining and Technology], Xiao-Peng Shen, Kui Han, Gang Tang

We studied the solvent effect on the geometric structure and (hyper)polarizability of spirobifluorene derivative by using quantum chemistry calculations. We found that the geometric structure is slightly affected by the solvent polarity. However, solvent polarity significantly influences first hyperpolarizability and second hyperpolarizability respectively.

- 2122 **Investigation on the mechanism for the binding and drug resistance of wild type and mutations of G86 residue in HIV-1 protease complexed with Darunavir by molecular dynamic simulation and free energy calculation**, Dan Li, Ying Zhang, Run-Ning Zhao, Song Fan, Ju-Guang Han [University of Science and Technology of China]

See Methodology/ Ligand Binding.

- 2121 **How well does cholesteryl hemisuccinate mimic cholesterol in saturated phospholipid bilayers?**, Waldemar Kulig, Joona Tynkkynen, Matti Javanainen, Moutusi Manna, Tomasz Rog, Ilpo Vattulainen, Pavel Jungwirth [Tampere University of Technology]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 2119 **Molecular simulation study of PAMAM dendrimer composite membranes**, Sepideh Amjad-Iranagh, Karim Golzar, Hamid Modarress [Amirkabir University of Technology]

Pure polysulfone (PSF) and its composites with chitosan (CST), hyaluronic acid (HA), conventional poly(amidoamine), and hydroxyl poly(amidoamine) dendrimers as the membranes for separation of the gases, methane, carbon dioxide, hydrogen sulfide, nitrogen, and oxygen have been studied by molecular dynamics (MD) and grand canonical Monte Carlo (GCMC) simulations.

- 2114 **Probing the electronic structures and properties of neutral and anionic $\text{ScSi}_n^{(0,-1)}$ ($n = 1-6$) clusters using ccCA-TM and G4 theory**, Jun Lu, Jucai Yang [Inner Mongolia University of Technology], Yali Kang, Hongmei Ning

The geometries, electronic structures and energies of small ScSi_n species ($n = 1-6$) and their anions have been systematically investigated by means of the higher level of the ccCA-TM, G4, and G4(MP2) schemes. The global minima of these clusters have been presented. The global minima of neutral ScSi_n ($n = 1-6$) and their anions are “substitutional structure” which is derived from Si_{n+1} by replacing a Si atom with a Sc atom.

- 2112 **First principles calculations of phenol adsorption on pristine and group III (B, Al, Ga) doped graphene layers** ,Yuliana Avila [Universidad Autónoma de Coahuila], Gregorio H. Coccoletzi, María Teresa Romero

We studied the doping effects on the electronic and structural properties of graphene upon interaction with phenol. Calculations were performed within the periodic density functional theory as implemented in PWscf code of the Quantum Espresso package. Graphene layers were modeled using 3×3 and 4×4 periodic supercells.

- 2110 **Quantum photonic base states: concept and molecular modeling. Managing chemical process descriptions beyond semi-classic schemes** ,O. Tapia [Uppsala University]

Four fundamental aspects bearing on molecular simulations are considered: (1) A different perception of quantum states; mappings from abstract Hilbert space down to laboratory levels; (2) Introduction of photon number Fock space; photonic bases tie together matter-to-photon quantum states: coherent photon-matter states. (3) Chemical tenets framed via photonic-base-states incorporating and defining multi-partite basis sets. (4) Entanglement provides a quantum-physical view connectable to a chemical bond concept.

- 2106 **The role of Cys179–Cys214 disulfide bond in the stability and folding of prion protein: insights from molecular dynamics simulations** ,Lulu Ning, Jingjing Guo, Nengzhi Jin, Huanxiang Liu, Xiaojun Yao [Lanzhou University]

See Applications / Protein Folding.

- 2105 **Structure and electronic properties of (+)-catechin: aqueous solvent effects** ,Erika N. Bentz, Alicia B. Pomilio, Rosana M. Lobayan [Universidad de la Cuenca del Plata]

We report a study of the structure of (+)-catechin, which belongs to the family of the flavan-3-ols—one of the five most widely distributed phenolic groups. The biological activities and pharmaceutical utility of these compounds are related to antioxidant activity due to their ability to scavenge free radicals.

- 2102 **Characterization of halogen...halogen interactions in crystalline dihalomethane compounds (CH_2Cl_2 , CH_2Br_2 and CH_2I_2): a theoretical study** ,Mehdi D. Esrafil [University of Maragheh], Mahshad Vakili, Mohammad Solimannejad

A theoretical study was performed to examine halogen...halogen ($\text{X}\cdots\text{X}$) bonds properties in crystalline dihalomethane CH_2X_2 compounds ($\text{X}=\text{Cl}$, Br and I). MP2/aug-cc-pVTZ calculations reveal that the interaction energies for CH_2X_2 dimers lie in the range between -3.7 and -9.9 kJ mol^{-1} .

- 2101 **Theoretical study of the complementarity in halogen-bonded complexes involving nitrogen and halogen as negative sites** ,Mehdi D. Esrafil [University of Maragheh] , Mahshad Vakili, Mohammad Solimannejad

This article analyzes the interplay between $\text{X}\cdots\text{N}$ and $\text{X}\cdots\text{X}$ halogen bonds interactions in $\text{NCX}\cdots\text{NCX}\cdots\text{XCH}_3$ complexes, where $\text{X}=\text{Cl}$ and Br . To better understand the properties of these systems, the corresponding dyads were also studied. These effects are studied theoretically in terms of geometric and energetic features of the complexes, which are computed by ab initio methods.

- 2097 **Structural flexibility of 4,4'-methylene diphenyl diisocyanate (4,4'-MDI): evidence from first principles calculations** ,Pawel Rodziewicz [University of Bialystok] , Jakub Goclon

A reactant used globally in the production of polyurethane is the molecule 4,4'-methylene diphenyl diisocyanate (4,4'-MDI). The structural flexibility of 4,4'-MDI is one of the most important molecular properties influencing the polymerization process and this property was therefore modeled using density functional theory (DFT) calculations and Car-Parrinello molecular dynamics (MD) simulations.

- 2094 **First-principles calculations of nickel, cadmium, and lead adsorption on a single-walled (10,0) carbon nanotube**, Mirele Bastos, Ihosvany Camps [Universidade Federal de Alfenas—Unifal-MG]

The adsorption of Ni, Cd, and Pb on a zigzag (10, 0) carbon nanotube (CNT) surface was investigated using density functional theory. Binding energy calculations were performed, and the results indicated that the three metals are stably adsorbed on the nanotube surface.

- 2093 **Theoretical study of the adsorption of pentachlorophenol on the pristine and Fe-doped boron nitride nanotubes**, Ruoxi Wang, Dongju Zhang [Shandong University], Rongxiu Zhu, Chengbu Liu

To explore the novel application of boron nitride nanotubes (BNNTs), we investigated the interaction of pentachlorophenol (PCP) pollutant with the pristine and Fe doped (Fe-doped) (8, 0) single-walled BNNTs by performing density functional theory calculations.

- 2091 **A DFT study of permanganate oxidation of toluene and its *ortho*-nitroderivatives**, Paweł Adamczyk, Reto S. Wijker, Thomas B. Hofstetter, Piotr Paneth [Lodz University of Technology]

Calculations of alternative oxidation pathways of toluene and its *ortho*-substituted nitro derivatives by permanganate anion have been performed. The competition between methyl group and ring oxidation has been addressed.

- 2089 **Influence of the nature of hydrogen halides and metal cations on the interaction types between borazine and hydrogen halides**, Hongying Zhuo, Qingzhong Li [Yantai University], Xiulin An, Wenzuo Li, Jianbo Cheng

The interactions between the H atom of borazine and hydrogen halide (HX, X = F, Cl, Br, and I) have been studied systematically. Four structures (a, b, c, and d) have been observed. The cyclic structure a is combined through a NH $\cdots$ X hydrogen bond and a BH $\cdots$ HX dihydrogen bond, a NH $\cdots$ X hydrogen bond and a BH $\cdots$ X halogen-hydride interaction are responsible for the cyclic structure b, structures c and d are maintained by a dihydrogen bond and a halogen-hydride interaction, respectively.

- 2086 **A periodic density functional theory study of tetrazole adsorption on anatase surfaces: potential application of tetrazole rings in dye-sensitized solar cells**, Alireza Najafi Chermahini [University of Technology], Behzad Hosseinzadeh, Alireza Salimi Beni, Abbas Teimouri, Mahmood Moradi

A density functional theory (DFT) method (periodic DMol³) with full geometry optimization was used to study the adsorption of tautomeric forms of tetrazole on anatase TiO₂ (101), (100), and (001) surfaces.

- 2085 **Computational quest for spherical C₁₂B₆₈ fullerenes with “magic” π -electrons and quasi-planar tetra-coordinated carbon**, Fengyu Li, De-en Jiang, Zhongfang Chen [University of Puerto Rico]

Inspired by the exciting properties of B₈₀ clusters and the novel chemical bonding of planar tetra-coordinated carbon (ptC), we computationally investigated C₁₂B₆₈ clusters by substituting 12 boron atoms to 12 carbon in the B₈₀ framework. Three types of C₁₂B₆₈ configurations, namely core-shell, boron-trapped and fullerene-like, were examined.

- 2084 **Structure and electronic properties of azadirachtin**, Elton A. S. de Castro [Av. Universitária s/n], Daniel A. B. de Oliveira, Sergio A. S. Farias, Ricardo Gargano, João B. L. Martins

We performed a combined DFT and Monte Carlo ¹³C NMR chemical-shift study of azadirachtin A, a triterpenoid that acts as a natural insect antifeedant. A conformational search using a Monte Carlo technique based on the RM1 semiempirical method was carried out in order to establish its preferred structure.

- 2081 **A DFT study of the unimolecular decomposition of 1,2,4-butanetriol trinitrate**, Weihua Zhu [Nanjing University of Science and Technology], Qingli Yan, Aimin Pang, Xuehui Chi, Xijuan Du, Heming Xiao

To improve understanding of the unimolecular decomposition mechanism of 1,2,4-butanetriol trinitrate (BTTN) in the gas phase, density functional theory calculations were performed to determine various decomposition pathways at the B3LYP/6-311G** level.

- 2075 **Molecular dynamic simulations reveal the mechanism of binding between xanthine inhibitors and DPP-4**, Yongliang Gu, Wei Wang, Xiaolei Zhu [Nanjing University of Technology], Keke Dong

See Applications / Ligand Binding.

- 2074 **Molecular properties of the PCO radical: heat of formation and the isomerization pathways**, Rommel B. Viana, Amanda R. Guimarães, Aguinaldo R. de Souza, Albérico B. F. da Silva [Universidade de São Paulo]

The potential energy surface of [P,C,O] system in the ground state was investigated by quantum chemical methods. Four different isomers were characterized at the B3LYP/aug-cc-pVTZ: COP (**i1**), cPCO (**i2**), PCO (**i3**), and CPO (**i4**). The linear species **i3** is the global minimum in the ground state surface, while **i4** is a bent structure, and **i2** is a cyclic isomer. In view to evaluate the bond nature of each isomer, a QTAIM and a NBO analyses were applied.

- 2070 **Exploration of the binding mode between (-)-zampanolide and tubulin using docking and molecular dynamics simulation**, Si-Yan Liao, Guang-Quan Mo [Guangzhou Medical University], Jin-Can Chen, Kang-Cheng Zheng

See Applications / Ligand Binding.

- 2068 **Conformational and coalescence behavior of trialkylphosphates in vacuum, water and dodecane**, A. S. Suneesh, G. V. S. Ashok Kumar, K. Gururaj, K. A. Venkatesan [Indira Gandhi Center for Atomic Research], M. C. Valsa Kumar, P. R. Vasudeva Rao

The conformations of trialkylphosphates (alkyl = propyl, butyl, pentyl and hexyl) in various diluents were studied by molecular dynamics simulations. The population density of various conformers of trialkylphosphate in different diluents such as water and n-dodecane was determined.

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- 2067 **Parallel implementation of 3D protein structure similarity searches using a GPU and the CUDA**
 ,Dariusz Mrozek[Silesian University of Technology], Miłosz Brożek, Bożena Małysiak-Mrozek

See Applications / Bioinformatics.

4. ADDRESSES OF PRINCIPAL AUTHORS

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About 135 Papers from more than 30 Journals are cited.

1	APPLICATIONS (94)	Page 2		
1.1	Small Molecules (15)			
	General and Model Systems	Page 2	Carbon Nanoparticles	Page 6
	Med. Chem. And Drug Design	Page 2		
1.2	Biopolymers (78)			
	Bioinformatics and Cheminformatics	Page 6	Enzyme Catalysis	Page 19
	Protein Structure Prediction	Page 7	Protein-Protein Interactions	Page 21
	Comparative or Homology Modeling	Page 9	Membrane Proteins	Page 22
	Protein Conformational Analysis	Page 11	Protein Folding	Page 24
	Protein Dynamics	Page 12	Protein-Nucleic Acids	Page 25
	Free Energy Calculations	Page 16	Nucleic Acids	Page 27
	Ligand Binding	Page 17		
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 29		
2	METHODOLOGY (24)	Page 29		
	QSAR	Page 29	QM & QM/MM	Page 32
	Molecular Dynamics	Page 30	Comparative or Homology	Page 35
	Monte Carlo	Page 31	Ligand Docking	Page 36
	Free Energy Perturbation	Page 31		
3	JOURNAL REVIEWS (5)	Page 37		
	Journal of Molecular Graphics and Modeling, 49, March, 2014.			
	Journal of Computational Chemistry, 35 (6), March, 2014.			
	Journal of Computational Chemistry, 35 (7), March, 2014.			
	Journal of Computational Chemistry, 35 (8), March, 2014.			
	Journal of Molecular Modeling, 20 (3), March, 2014.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 51		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

Liquid-Liquid Extraction of Uranyl by TBP: The TBP and Ions Models and Related Interfacial Features Revisited by MD and PMF Simulations

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J. Phys. Chem. B., **118**, 3133–3149, 2014.

We report a molecular dynamics (MD) study of biphasic systems involved in the liquid-liquid extraction of uranyl nitrate by tri-n-butylphosphate (TBP) to hexane, from “pH neutral” or acidic (3 M nitric acid) aqueous solutions, to assess the model dependence of the surface activity and partitioning of TBP alone, of its $\text{UO}_2(\text{NO}_3)_2(\text{TBP})_2$ complex, and of $\text{UO}_2(\text{NO}_3)_2$ or UO_2^{2+} uncomplexed. For this purpose, we first compare several electrostatic representations of TBP with regards to its polarity and conformational properties, its interactions with H_2O , HNO_3 , and $\text{UO}_2(\text{NO}_3)_2$ species, its relative free energies of solvation in water or oil environments, the properties of the pure TBP liquid and of the pure-TBP/water interface.

Medicinal Chemistry and Drug Design

Structure-based screening of inhibitors against KPC-2: designing potential drug candidates against multidrug-resistant bacteria

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J. Biomol. Stru. and Dyn., **32**, 741-750, 2014.

KPC-2 β -lactamase demonstrates a wide substrate spectrum that includes carbapenemases, oxyimino-cephalosporins, and cephamycins. In addition, strains harboring KPC-type β -lactamases are often identified as resistant to standard β -lactamase inhibitors. Thus, KPC-2 carbapenems present a significant clinical challenge, as the mechanistic bases for KPC-2-associated phenotypes remain mysterious. Inhibiting the function of these resistance enzymes could control the hydrolysis of antibiotics. In the present study, we have reported two novel (non- β -lactam) compounds that inhibit the activity of the KPC-2 enzyme. These compounds were identified by structure-based virtual screening using computational docking programs and molecular dynamics simulations with the solved crystal structure.



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Medicinal Chemistry and Drug Design (Cont'd)

Interchain hydrophobic clustering promotes rigidity in HIV-1 protease flap dynamics: new insights from Molecular Dynamics

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J. Biomol. Stru. and Dyn., 32, 899-915, 2014.

The dynamics of HIV-1 protease (HIV-pr), a drug target for HIV infection, has been studied extensively by both computational and experimental methods. The flap dynamics of HIV-pr is considered to be more important for better ligand binding and enzymatic actions. Moreover, it has been demonstrated that the drug-induced mutations can change the flap dynamics of HIV-pr affecting the binding affinity of the ligands. Therefore, detailed understanding of flap dynamics is essential for designing better inhibitors.

A 3D structural model and dynamics of hepatitis C virus NS3/4A protease (genotype 4a, strain ED43) suggest conformational instability of the catalytic triad: implications in catalysis and drug resistivity

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J. Biomol. Stru. and Dyn., 32, 950-958, 2014.

Egypt has the highest prevalence of hepatitis C virus (HCV) infection worldwide with a frequency of 15%. The protease domain of the HCV nonstructural protein 3 (NS3) has been targeted for inhibition by several drugs. This approach has had marked success in inhibiting genotype 1 (HCV-1), the predominant genotype in the USA, Europe, and Japan. However, HCV-4a was found to resist inhibition by a number of these drugs, and little progress has been made to understand the structural basis of its drug resistivity. As a step forward, we sequenced the NS3 HCV-4a protease gene (strain ED43) and subsequently built a 3D structural model threaded through a template crystal structure of HCV-1b NS3 protease.

Molecular Dynamics Simulations and Structure-Based Rational Design Lead to Allosteric HCV NS5B Polymerase Thumb Pocket 2 Inhibitor with Picomolar Cellular Replicon Potency

Oliver Huckle [Boehringer Ingelheim (Canada) Ltd], René Coulombe, Pierre Bonneau, Mélanie Bertrand-Laperle, Christian Brochu, James Gillard, Marc-André Joly, Serge Landry, Olivier Lepage, Montse Llinàs-Brunet, Marc Pesant, Martin Poirier, Maude Poirier, Ginette McKercher, Martin Marquis, George Kukolj, Pierre L. Beaulieu, Timothy A. Stammers

J. Med. Chem., 57, 1932–1943, 2014.

The design and preliminary SAR of a new series of 1H-quinazolin-4-one (QAZ) allosteric HCV NS5B thumb pocket 2 (TP-2) inhibitors was recently reported. To support optimization efforts, a molecular dynamics (MD) based modeling workflow was implemented, providing information on QAZ binding interactions with NS5B. This approach predicted a small but critical ligand-binding induced movement of a protein backbone region which increases the pocket size and improves access to the backbone carbonyl groups of Val 494 and Pro 495.

Discovery of potent inhibitor for matrix metalloproteinase-9 by pharmacophore based modeling and dynamics simulation studies

Sukesh Kalva, E.R. Azhagiya Singam, V. Rajapandian, Lilly M. Saleena, V. Subramanian [Council of Scientific and Industrial Research, Adyar]

J. Mol. Graph. and Mod., 49, 25-37, 2014.

Matrix metalloproteinase-9 (MMP-9) is an attractive target for anticancer therapy. In the present study ligand based pharmacophore modeling was performed to elucidate the structural elements for a diverse class of MMP-9 inhibitors. The pharmacophore model was validated through Güner-Henry (GH) scoring method. The final pharmacophore model consisted of three hydrogen bond acceptors (HBA), and two ring aromatic regions (RA). This model was utilized to screen the natural compound database to seek novel compounds as MMP-9 inhibitors.

Medicinal Chemistry and Drug Design (Cont'd)

Pharmacophore model of the quercetin binding site of the SIRT6 protein

S. Ravichandran, N. Singh, D. Donnelly, M. Migliore, P. Johnson, C. Fishwick, B.T. Luke, B. Martin, S. Maudsley, S.D. Fugmann, R. Moaddel [National Institute on Aging]

J. Mol. Graph. and Mod., **49**, 38–46, 2014.

SIRT6 is a histone deacetylase that has been proposed as a potential therapeutic target for metabolic disorders and the prevention of age-associated diseases. The previous study generated a preliminary pharmacophore for the quercetin binding site on SIRT6, containing 3 hydrogen bond donors and one hydrogen bond acceptor. In this study, we have generated a refined pharmacophore with an additional twelve quercetin analogs. The resulting model had a positive linear behavior between the experimental elution time verses the fit values obtained from the model with a correlation coefficient of 0.8456.

Discovery of novel anti-leishmanial agents targeting LdLip3 lipase

Saravanan Parameswaran, Prakash Saudagar, Vikash Kumar Dubey, Sanjukta Patra [Indian Institute of Technology Guwahati]

J. Mol. Graph. and Mod., **49**, 68–79, 2014.

Leishmaniasis is a neglected tropical disease, caused by several species of *Leishmania*. Being an opportunistic lipid-scavenging pathogen, *Leishmania* relies extensively on lipid metabolism especially for host–pathogen interaction, utilizing host lipids for energy and virulence. The rational approach is to target lipid metabolism of the pathogen focusing lipid-catabolizing lipases. The LdLip3 lipase is considered as drug target as it is constitutively expressed in both promastigote and amastigote forms. Since the LdLip3 structure is not known, we modeled its three-dimensional structure to implement structure-based drug discovery approach.

Insights into the influence of 5-HT_{2C} aminoacidic variants with the inhibitory action of serotonin inverse agonists and antagonists

Roberta Galeazzi [Dipartimento di Scienze della Vita e dell'Ambiente- Università Politecnica delle Marche], Luca Massaccesi, Francesco Piva, Giovanni Principato, Emilioano Laudadio

J. Mol. Mod., **20**, 2120, 2014.

Specific modulation of serotonin 5-HT_{2C} G protein-coupled receptors may be therapeutic for obesity and neuropsychiatric disorders. The different efficacy of drugs targeting these receptors are due to the presence of genetic variants in population and this variability is still hard to predict. Therefore, in order to administer the more suitable drug, taking into account patient genotype, it is necessary to know the molecular effects of its gene nucleotide variations. In this work, starting from an accurate 3D model of 5-HT_{2C}, we focus on the prediction of the possible effect of some single nucleotide polymorphisms (SNPs) producing amino acid changes in proximity of the 5-HT_{2C} ligand binding site.

Discovery of New Liver X Receptor Agonists by Pharmacophore Modeling and Shape-Based Virtual Screening

Veronika Temml, Constance V. Voss, Verena M. Dirsch, Daniela Schuster [University of Innsbruck]

J. Chem. Infor. and Mod. **54**, 367–371, 2014.

Agonists of liver X receptors (LXR) α and β are important regulators of cholesterol metabolism, but agonism of the LXR α subtype appears to cause hepatic lipogenesis, suggesting LXR β -selective activators are attractive new lipid lowering drugs. In this work, pharmacophore modeling and shape-based virtual screening were combined to predict new LXR β -selective ligands. Out of the 10 predicted compounds, three displayed significant LXR activity. Two activated both LXR subtypes. The third compound activated LXR β 1.8-fold over LXR α .

Medicinal Chemistry and Drug Design (Cont'd)

ZINClick: A Database of 16 Million Novel, Patentable, and Readily Synthesizable 1,4-Disubstituted Triazoles

Alberto Massarotti [Università degli Studi del Piemonte Orientale], Angelo Brunco, Giovanni Sorba, Gian Cesare Tron

J.Chem. Infor. and Mod. **54**, 396–406, 2014.

Since Professors Sharpless, Finn, and Kolb first introduced the concept of “click reactions” in 2001 as powerful tools in drug discovery, 1,4-disubstituted-1,2,3-triazoles have become important in medicinal chemistry due to the simultaneous discovery by Sharpless, Fokin, and Meldal of a perfect click 1,3-dipolar cycloaddition reaction between azides and alkynes catalyzed by copper salts. Because of their chemical features, these triazoles are proposed to be aggressive pharmacophores that participate in drug-receptor interactions while maintaining an excellent chemical and metabolic profile. Surprisingly, no virtual libraries of 1,4-disubstituted-1,2,3-triazoles have been generated for the systematic investigation of the click-chemical space.

Pathway Analysis for Drug Repositioning Based on Public Database Mining

Yongmei Pan, Tiejun Cheng, Yanli Wang [National Institutes of Health, 8600 Rockville Pike] Stephen H. Bryant

J.Chem. Infor. and Mod. **54**, 407–418, 2014.

Sixteen FDA-approved drugs were investigated to elucidate their mechanisms of action (MOAs) and clinical functions by pathway analysis based on retrieved drug targets interacting with or affected by the investigated drugs. Protein and gene targets and associated pathways were obtained by data-mining of public databases including the MMDb, PubChem BioAssay, GEO DataSets, and the BioSystems databases. Entrez E-Utilities were applied, and in-house Ruby scripts were developed for data retrieval and pathway analysis to identify and evaluate relevant pathways common to the retrieved drug targets. Pathways pertinent to clinical uses or MOAs were obtained for most drugs.

Multiple e-Pharmacophore Modeling, 3D-QSAR, and High-Throughput Virtual Screening of Hepatitis C Virus NS5B Polymerase Inhibitors

Patrishia Joseph Therese, Dinesh Manvar, Sridevi Kondepudi, Madhu Babu Battu, Dharmarajan Sriram, Amartya Basu, Perumal Yogeewari, Neerja Kaushik-Basu [Rutgers Cancer Institute of New Jersey]

J.Chem. Infor. and Mod. **54**, 539–552, 2014.

The hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase (RdRP) is a crucial and unique component of the HCV RNA replication machinery and a validated target for drug discovery. Multiple crystal structures of NS5B inhibitor complexes have facilitated the identification of novel compound scaffolds through in silico analysis. With the goal of discovering new NS5B inhibitor leads, HCV NS5B crystal structures bound with inhibitors in the palm and thumb allosteric pockets in combination with ligands with known inhibitory potential were explored for a comparative pharmacophore analyses.

Computational Study on the Drug Resistance Mechanism against HCV NS3/4A Protease Inhibitors Vaniprevir and MK-5172 by the Combination Use of Molecular Dynamics Simulation, Residue Interaction Network, and Substrate Envelope Analysis

Weiwei Xue, Yihe Ban, Huanxiang Liu, Xiaojun Yao [Lanzhou University]

J.Chem. Infor. and Mod. **54**, 621–633, 2014.

A detailed understanding of drug resistance mechanism to vaniprevir and MK-5172 is therefore very crucial for the design of novel potent agents targeting viral variants. In this work, molecular dynamics (MD) simulation, binding free energy calculation, free energy decomposition, residue interaction network (RIN), and substrate envelope analysis were used to study the detailed drug resistance mechanism of the three mutants R155K, A156T, and D168A to vaniprevir and MK-5172. MD simulation was used to investigate the binding mode for these two inhibitors to wild-type and resistant mutants of HCV NS3/4A protease.

Carbon Nanoparticles

Dispersion of Carbon Nanotubes Using Mixed Surfactants: Experimental and Molecular Dynamics Simulation Studies

B. Sohrabi [Iran University of Science and Technology], N. Poorgholami-Bejarpasi, N. Nayeri

J. Phys. Chem. B., **118**, 3094–3103, 2014.

The ability of cationic-rich and anionic-rich mixtures of CTAB (cetyltrimethylammonium bromide) and SDS (sodium dodecyl sulfate) for dispersing of carbon nanotubes (CNTs) in aqueous media has been studied through both the experimental and molecular dynamics simulation methods. Compared to the pure CTAB and SDS, these mixtures are more effective with the lower concentrations and more individual CNTs, reflecting a synergistic effect in these mixtures. The synergistic effects observed in mixed surfactant systems are mainly due to the electrostatic attractions between surfactant heads. In addition, the surface charge related to the colloidal stability of mixed surfactant-covered nanotubes has been characterized by means of ζ -potential measurements.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Implementation of the Hungarian Algorithm to Account for Ligand Symmetry and Similarity in Structure-Based Design

William J. Allen ,Robert C. Rizzo [Stony Brook University]

J.Chem. Infor. and Mod. **54**, 518–529, 2014.

False negative docking outcomes for highly symmetric molecules are a barrier to the accurate evaluation of docking programs, scoring functions, and protocols. This work describes an implementation of a symmetry-corrected root-mean-square deviation (RMSD) method into the program DOCK based on the Hungarian algorithm for solving the minimum assignment problem, which dynamically assigns atom correspondence in molecules with symmetry. The algorithm adds only a trivial amount of computation time to the RMSD calculations and is shown to increase the reported overall docking success rate by approximately 5% when tested over 1043 receptor–ligand systems.

LIBSA – A Method for the Determination of Ligand-Binding Preference to Allosteric Sites on Receptor Ensembles

Harrison J. Hocker, Nandini Rambahal, Alemayehu A. Gorfe [The University of Texas Health Science Center at Houston]

J.Chem. Infor. and Mod. **54**, 530–538, 2014.

We have developed a protocol, termed LIBSA for LIgand Binding Specificity Analysis, that analyzes multiple docked poses against a single or ensemble of receptor conformations and returns a metric for the relative binding to a specific region of interest. By using novel filtering algorithms and the signal-to-noise ratio (SNR), the relative ligand-binding frequency at different pockets can be calculated and compared quantitatively. Ligands can then be triaged by their tendency to bind to a site instead of ranking by affinity alone.

Bioinformatics and Cheminformatics (Cont'd)

Flexibility and Explicit Solvent in Molecular-Dynamics-Based Docking of Protein–Glycosaminoglycan Systems

Sergey A. Samsonov, Jan-Philip Gehrcke, M. Teresa Pisabarro [BIOTEC, TU Dresden]

J.Chem. Infor. and Mod. **54**, 582–592, 2014.

We present Dynamic Molecular Docking (DMD), a novel targeted molecular dynamics-based protocol developed to address ligand and receptor flexibility as well as the inclusion of explicit solvent in local molecular docking. A class of ligands for which docking performance especially benefits from overcoming these challenges is the glycosaminoglycans (GAGs). GAGs are periodic, highly flexible, and negatively charged polysaccharides playing an important role in the extracellular matrix via interaction with proteins such as growth factors and chemokines.

Coarse Grained Models Reveal Essential Contributions of Topological Constraints to the Conformational Free Energy of RNA Bulges

Anthony M. Mustoe, Hashim M. Al-Hashimi, Charles L. Brooks, III [University of Michigan]

J. Phys. Chem. B., **118**, 2615–2627, 2014.

Here we develop a new coarse-grain model, TOPRNA, that is optimized for exploring detailed aspects of these topological constraints in complex RNA systems. Unlike prior models, TOPRNA effectively treats RNAs as collections of semirigid helices linked by freely rotatable single strands, allowing us to isolate the effects of secondary structure connectivity and sterics on 3D structure. Simulations of bulge junctions show that TOPRNA captures new aspects of topological constraints, including variations arising from deviations in local A-form structure, translational displacements of the helices, and stereochemical constraints imposed by bulge-linker nucleotides.

Protein Structure Prediction

SSThread: Template-free protein structure prediction by threading pairs of contacting secondary structures followed by assembly of overlapping pairs

Kevin J. Maurice [15 Mitchell Ave]

J. Comp. Chem., **35**, 644–656, 2014.

Acquiring the three-dimensional structure of a protein from its amino acid sequence alone, despite a great deal of work and significant progress on the subject, is still an unsolved problem. SSThread, a new template-free algorithm is described here that consists of making several predictions of contacting pairs of α -helices and β -strands derived from a database of experimental structures using a knowledge-based potential, secondary structure prediction, and contact map prediction followed by assembly of overlapping pair predictions to create an ensemble of core structure predictions whose loops are then predicted.

Protein Structure Prediction (Cont'd)

Protein Structure Refinement of CASP Target Proteins Using GNEIMO Torsional Dynamics Method

Adrien B. Larsen, Jeffrey R. Wagner, Abhinandan Jain, Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J.Chem. Infor. and Mod. **54**, 508–517, 2014.

A longstanding challenge in using computational methods for protein structure prediction is the refinement of low-resolution structural models derived from comparative modeling methods into highly accurate atomistic models useful for detailed structural studies. We have applied GNEIMO with temperature replica exchange to refine low-resolution protein models of 30 proteins taken from the continuous assessment of structure prediction (CASP) competition. We have shown that GNEIMO torsional MD method leads to refinement of up to 1.3 Å in the root-mean-square deviation in coordinates for 30 CASP target proteins without using any experimental data as restraints in performing the GNEIMO simulations.

SVR_CAF: An integrated score function for detecting native protein structures among decoys

Jianhong Zhou, Wenying Yan, Guang Hu ,Bairong Shen [Soochow University]

Proteins: Stru. Fun. & Bioinf., **82**, 556–564, 2014.

An accurate score function for detecting the most native-like models among a huge number of decoy sets is essential to the protein structure prediction. In this work, we developed a novel integrated score function (SVR_CAF) to discriminate native structures from decoys, as well as to rank near-native structures and select best decoys when native structures are absent. SVR_CAF is a machine learning score, which incorporates the contact energy based score (CE_score), amino acid network based score (AAN_score), and the fast Fourier transform based score (FFT_score).

BCL::Fold—Protein topology determination from limited NMR restraints

Brian E. Weiner, Nathan Alexander, Louesa R. Akin, Nils Woetzel, Mert Karakas Jens Meiler [Vanderbilt University]

Proteins: Stru. Fun. & Bioinf., **82**, 587–595, 2014.

When experimental protein NMR data are too sparse to apply traditional structure determination techniques, *de novo* protein structure prediction methods can be leveraged. Here, we describe the incorporation of NMR restraints into the protein structure prediction algorithm BCL::Fold. The method assembles discreet secondary structure elements using a Monte Carlo sampling algorithm with a consensus knowledge-based energy function. New components were introduced into the energy function to accommodate chemical shift, nuclear Overhauser effect, and residual dipolar coupling data.

Comparative or Homology Modeling

Understanding the evolutionary relationship of hemagglutinin protein from influenza viruses using phylogenetic and molecular modeling studies

Muthusamy Karthikeyan [Alagappa University], Palani Kirubakaran, Kh. Dhanachandra Singh, Bhuvaneshwari Sampath, Gopinath Krishnasamy

J. Biomol. Stru. and Dyn., 32, 816-830, 2014.

In this study, sequence and phylogenetic analysis of the H1N1 (2009) HA, from Mexico City along with 1952 sequences, from different subtypes of pandemic influenza A virus were studied and results showed that the closest relationship of H1N1 (2009) Mexico strain was with the H1N1 (2007) Mallard Norway strain. Analysis of secondary structures predicted from the protein sequence revealed that diminishing of alpha helixes was observed in many areas of the sequences between the years 2005 to 2010. Conversely, analysis at the structural level is necessary to critically assess the functional significance. Structural level investigation was therefore done for the above said proteins by constructing the 3D structure of these proteins through homology modeling.

Comparative molecular dynamics simulation studies for determining factors contributing to the thermostability of chemotaxis protein "CheY"

Manish Paul, Mousumi Hazra, Arghya Barman, Saugata Hazra [Albert Einstein College of Medicine]

J. Biomol. Stru. and Dyn., 32, 928-949, 2014.

Comparative molecular dynamics simulations of chemotaxis protein "CheY" from thermophilic origin *Thermotoga maritima* and its mesophilic counterpart *Salmonella enterica* have been performed for 10 ns each at 300 and 350 K, and 20 ns each at 400 and 450 K. The trajectories were analyzed in terms of different factors like root-mean-square deviation, root-mean-square fluctuation, radius of gyration, solvent accessible surface area, H-bonds, salt bridge content, and protein-solvent interactions which indicate distinct differences between the two of them. The two proteins also follow dissimilar unfolding pathways. The overall flexibility calculated by the trace of the diagonalized covariance matrix displays similar flexibility of both the proteins near their optimum growth temperatures.

Toward activated homology models of the human M₁ muscarinic acetylcholine receptor

Sek Peng Chin, Michael J.C. Buckle [University of Malaya], David K. Chalmers, Elizabeth Yuriev, Stephen W. Doughty

J. Mol. Graph. and Mod., 49, 91-98, 2014.

Structure-based virtual screening offers a good opportunity for the discovery of selective M₁ muscarinic acetylcholine receptor (mAChR) agonists for the treatment of Alzheimer's disease. However, no 3-D structure of an M₁ mAChR is yet available and the homology models that have been previously reported are only able to identify antagonists in virtual screening experiments. In this study, we generated a homology model of the human M₁ mAChR, based on the crystal structure of an M₃ mAChR as the template.

Comparative or Homology Modeling (Cont'd)

Sequence and 3D structure based analysis of TNT degrading proteins in *Arabidopsis thaliana*

Amrita Bhattacharjee, Rahul Shubhra Mandal, Santasabuj Das, Sudip Kundu [University of Calcutta]

J. Mol.Mod., **20**, 2174, 2014.

TNT, accidentally released at several manufacturing sites, contaminates ground water and soil. It has a toxic effect to algae and invertebrate, and chronic exposure to TNT also causes harmful effects to human. On the other hand, many plants including *Arabidopsis thaliana* have the ability to metabolize TNT either completely or at least to a reduced less toxic form. In *A. thaliana*, the enzyme UDP glucosyltransferase (UDPGT) can further conjugate the reduced forms 2-HADNT and 4-HADNT (2-hydroxylamino-4, 6- dinitrotoluene and 4-hydroxylamino-2, 6- dinitrotoluene) of TNT. Based on the experimental analysis, existing literature and phylogenetic analysis, it is evident that among 107 UDPGT proteins only six are involved in the TNT degrading process.

Homology modeling, molecular dynamics and atomic level interaction study of snake venom 5' nucleotidase

A. Syed Yasir Arafat, A. Arun, M. Ilamathi, J. Asha, P. R. Sivashankari, Cletus J. M. D'Souza, V. Sivaramakrishnan [SASTRA Universit], B. L. Dhananjaya

J. Mol.Mod., **20**, 2156, 2014.

5' Nucleotidase (5' NUC) is a ubiquitously distributed enzyme known to be present in snake venoms (SV) that is responsible primarily for causing dysregulation of physiological homeostasis in humans by inducing anticoagulant effects and by inhibiting platelet aggregation. It is also known to act synergistically with other toxins to exert a more pronounced anti-coagulant effect during envenomation. Its structural and functional role is not yet ascertained clearly. The 3D structure of snake venom 5' nucleotidase (SV-5' NUC) is not yet known and was predicted by us for the first time using a comparative homology modeling approach using *Demansia vestigiata* protein sequence.

In silico analysis on structure and DNA binding mode of AtNAC1, a NAC transcription factor from *Arabidopsis thaliana*

Qiankun Zhu, Jiabin Zou, Mengli Zhu, Zubi Liu, Peichun Feng, Gaotao Fan, Wanjuan Wang, Hai Liao

J. Mol.Mod., **20**, 2117, 2014.

NAC (NAM/ATAF/CUC) transcription factors regulate the expression of the target genes by formation of NAC-DNA complex, which are involved in development, stress responses and nutrient distribution in many metapophyta plants. AtNAC1, a NAC transcription factor from *Arabidopsis thaliana*, plays an important role in auxin signaling and root development. In order to understand the structure and DNA binding model of AtNAC1, the 3D structure model of AtNAC1 was constructed and docked with its target DNA. The structure of AtNAC1 monomer contained four α -helices and eight β -sheets.

Homology modeling and virtual screening for antagonists of protease from yellow head virus

Sasimanas Unajak, Orathai Sawatdichaikul, Napat Songtawee, Siriluk Rattanabunyong, Anchalee Tassnakajon, Nontawith Areechon, Ikuo Hirono, Hidehiro Kondo, Pongsak Khunrae, Triwit Rattanaojpong, Kiattawee Choowongkomon [Kasetsart University]

J. Mol.Mod., **20**, 2116, 2014.

In this study, a theoretical modeling of the YHV protease was constructed based on the folds of several known crystal structures of other viral proteases, and was subsequently used as a target for virtual screening—molecular docking against approximately 1364 NCI structurally diversity compounds. A complex between the protease and the hit compounds was investigated for intermolecular interactions by molecular dynamics simulations.

Protein Conformational Analysis

A Conformational Ensemble Derived Using NMR Methyl Chemical Shifts Reveals a Mechanical Clamping Transition That Gates the Binding of the HU Protein to DNA

Arvind Kannan, Carlo Camilloni, Aleksandr B. Sahakyan, Andrea Cavalli, Michele Vendruscolo [University of Cambridge]

J. Am. Chem. Soc., 2013, **136**, 2204–2207, 2014.

Recent improvements in the accuracy of structure-based methods for the prediction of nuclear magnetic resonance chemical shifts have inspired numerous approaches for determining the secondary and tertiary structures of proteins. Such advances also suggest the possibility of using chemical shifts to characterize the conformational fluctuations of these molecules. Here we describe a method of using methyl chemical shifts as restraints in replica-averaged molecular dynamics (MD) simulations, which enables us to determine the conformational ensemble of the HU dimer and characterize the range of motions accessible to its flexible β -arms.

Importance of ligand conformational energies in carbohydrate docking: Sorting the wheat from the chaff

Anita K. Nivedha, Spandana Makeneni, Bethany Lachele Foley, Matthew B. Tessier, Robert J. Woods [National University of Ireland]

J. Comp. Chem., 35, 526–539, 2014.

Docking algorithms that aim to be applicable to a broad range of ligands suffer reduced accuracy because they are unable to incorporate ligand-specific conformational energies. Here, we develop a set of Carbohydrate Intrinsic (CHI) energy functions that quantify the conformational properties of oligosaccharides, based on the values of their glycosidic torsion angles. The relative energies predicted by the CHI energy functions mirror the conformational distributions of glycosidic linkages determined from a survey of oligosaccharide-protein complexes in the protein data bank.

A comprehensive conformational analysis of tryptophan, its ionic and dimeric forms

Uppula Purushotham, G. Narahari Sastry [CSIR-Indian Institute of Chemical Technology]

J. Comp. Chem., 35, 595–610, 2014.

Tryptophan is an essential amino acid, and understanding the conformational preferences of monomer and dimer is a subject of outstanding relevance in biological systems. An exhaustive first principles investigation of tryptophan (**W**) and its ionized counterparts cations (**WC**), anions (**WA**), and zwitterions (**WZ**) has been carried out. A comprehensive and systematic study of tryptophan dimer (**WD**) conformations resulted in about 62 distinct minima on the potential energy surface.

Modified Amber Force Field Correctly Models the Conformational Preference for Tandem GA pairs in RNA

Asaminew H. Aytenfisu, Aleksandar Spasic, Matthew G. Seetin, John Serafini, David H. Mathews [University of Rochester Medical Center]

J. Chem. Theor. and Comp., **10**, 1292–1301, 2014.

Molecular mechanics with all-atom models was used to understand the conformational preference of tandem guanine-adenine (GA) noncanonical pairs in RNA. These tandem GA pairs play important roles in determining stability, flexibility, and structural dynamics of RNA tertiary structures. Previous solution structures showed that these tandem GA pairs adopt either imino (cis Watson-Crick/Watson-Crick A-G) or sheared (trans Hoogsteen/sugar edge A-G) conformations depending on the sequence and orientation of the adjacent closing base pairs. The solution structures (GCGGACGC)₂ [Biochemistry, 1996, 35, 9677–9689] and (GCGGAUGC)₂ [Biochemistry, 2007, 46, 1511–1522] demonstrate imino and sheared conformations for the two central GA pairs, respectively.

Protein Conformational Analysis (Cont'd)

Self-Assembly of an Aspartate-Rich Sequence from the Adenovirus Fiber Shaft: Insights from Molecular Dynamics Simulations and Experiments

Phanourios Tamamis, Konstantina Terzaki, Michalis Kassinos, Lefteris Mastrogiannis, Estelle Mossou, V. Trevor Forsyth, Edward P. Mitchell, Anna Mitraki [University of Cyprus], Georgios Archontis

J. Phys. Chem. B., **118**, 1765–1774, 2014.

The self-assembly of short peptides into fibrous nanostructures (such as fibrils and tubes) has recently become the subject of intense theoretical and experimental scrutiny, as such assemblies are promising candidates for nanobiotechnological applications. The sequences of natural fibrous proteins may provide a rich source of inspiration for the design of such short self-assembling peptides. We describe the self-assembly of the aspartate-rich undecapeptide (NH₃⁺-LSGSDSDLTV-NH₂), a sequence derived from the shaft of the adenovirus fiber. We demonstrate that the peptide assembles experimentally into amyloid-type fibrils according to widely accepted diagnostic criteria.

Conformational Properties of α - or β -(1→6)-Linked Oligosaccharides: Hamiltonian Replica Exchange MD Simulations and NMR Experiments

Dhilon S. Patel, Robert Pendrill, Sairam S. Mallajosyula, Göran Widmalm [Stockholm University], Alexander D. MacKerell, Jr.

J. Phys. Chem. B., **118**, 2851–2871, 2014.

Conformational sampling for a set of 10 α - or β -(1→6)-linked oligosaccharides has been studied using explicit solvent Hamiltonian replica exchange (HREX) simulations and NMR spectroscopy techniques. Validation of the force field and simulation methodology is done by comparing calculated transglycosidic J coupling constants and proton–proton distances with the corresponding NMR data. Initial calculations showed poor agreement, for example, with >3 Hz deviation of the calculated 3J(H5,H6R) values from the experimental data, prompting optimization of the ω torsion angle parameters associated with (1→6)-linkages.

Protein Dynamics

Sequence-based Gaussian network model for protein dynamics

Hua Zhang [Zhejiang Gongshang University], Lukasz Kurgan

Bioinformatics. **30**, 497–505, 2014.

Gaussian network model (GNM) is widely adopted to analyze and understand protein dynamics, function and conformational changes. The existing GNM-based approaches require atomic coordinates of the corresponding protein and cannot be used when only the sequence is known.

We report, first of its kind, GNM model that allows modeling using the sequence. Our linear regression-based, parameter-free, sequence-derived GNM (LpfSeqGNM) uses contact maps predicted from the sequence and models local, in the sequence, contact neighborhoods with the linear regression.

Protein Dynamics (Cont'd)

Charge Invariant Protein–Water Relaxation in GB1 via Ultrafast Tryptophan Fluorescence

Arianna Biesso, Jianhua Xu, Pedro L. Muñoz, Patrik R. Callis, Jay R. Knutson [National Institutes of Health, Bethesda]

J. Am. Chem. Soc., 2013, **136**, 2739–2747, 2014.

The protein–water interface is a critical determinant of protein structure and function, yet the precise nature of dynamics in this complex system remains elusive. The small protein GB1 contains a single Trp (W43) of this type, and its structure is refractory to pH above 3. Thus, it can be used to examine the dependence of dipolar relaxation upon charge reconfiguration with titration. Somewhat surprisingly, the dipolar dynamics in the 100 fs to 100 ps range were unchanged with pH, although nanosecond yield, rates, and access all changed. These results were rationalized with the help of molecular dynamics (including QM-MM) simulations that reveal a balancing, sometimes even countervailing influence of protein and water dipoles.

pH-Induced Stability Switching of the Bacteriophage HK97 Maturation Pathway

Eric R. May, Karunesh Arora, and Charles L. Brooks, III [University of Michigan]

J. Am. Chem. Soc., 2013, **136**, 3097–3107, 2014.

Many viruses undergo large-scale conformational changes during their life cycles. Blocking the transition from one stage of the life cycle to the next is an attractive strategy for the development of antiviral compounds. In this work, we have constructed an icosahedrally symmetric, low-energy pathway for the maturation transition of bacteriophage HK97. By conducting constant-pH molecular dynamics simulations on this pathway, we identify which residues are contributing most significantly to shifting the stability between the states along the pathway under differing pH conditions.

Modelling and analysis of early aggregation events of BMHP1-derived self-assembling peptides

Gloria Anna Ada Saracino, Fabrizio Gelain [Center of Nanomedicine and Tissue Engineering A. O. Ospedale Niguarda Ca' Granda, Milan]

J. Biomol. Stru. and Dyn., **32**, 759-775, 2014.

In this study, the effects of biotinylation on the self-assembly dynamics of seven BMHP1-derived SAPs have been investigated by molecular dynamics simulations. We confirmed that these SAPs self-assemble into β -structures and that proline acts as a β -breaker of the assembled aggregates. In biotinylated peptides, the formation of ordered β -structured aggregates is triggered by both the establishment of a dense and dynamic H-bonds network and the formation of a 'hydrophobic wall' available to interact with other peptides.

Decoding the components of dynamics in three-domain proteins

Mateusz Maciejewski, Paul N. Barlow, Nico Tjandra [National Institutes of Health, Bethesda]

J. Comp. Chem., **35**, 518–525, 2014.

In this study, we examine the feasibility and limitations of describing the motional behavior of three-domain proteins in which the domains are linearly connected. In addition to attempting the determination of the internal and overall reorientational correlation times, we investigate the existence of correlations in the motions between the three domains. Since in linearly arranged three-domain proteins, there are typically no experimental data that can directly report on motional correlation between the first and the third domain, we address this question by dynamics simulations.

Protein Dynamics (Cont'd)

ReaxFF molecular dynamics simulations of the initial pyrolysis mechanism of unsaturated triglyceride

Zhiqiang Zhang [Taiyuan University of Technology], Kefeng Yan, Jilong Zhang

J. Mol.Mod., **20**, 2127, 2014.

To understand the impact of C = C double bonds in acyl chains of unsaturated triglycerides on the reaction mechanism and product composition in their initial pyrolysis process, ReaxFF molecular dynamics simulations were carried out using a molecular model, trilinolenin, at temperatures of 2000, 2250, and 2500 K. Analyses indicated that the observed pyrolysis mechanisms of unsaturated triglyceride are nearly identical to the saturated triglyceride, and the pyrolysis products also include alkanes, alkenes, alkadienes, aromatics, oxygenated species, CO₂, and H₂.

Targeted studies on the interaction of nicotine and morin molecules with amyloid β -protein

Subramaniam Boopathi, Ponmalai Kolandaivel [Bharathiar University]

J. Mol.Mod., **20**, 2109, 2014.

Alzheimer's disease (AD) is a neurodegenerative disorder that occurs due to progressive deposition of amyloid β -protein (A β) in the brain. Stable conformations of solvated A β ₁₋₄₂ protein were predicted by molecular dynamics (MD) simulation using the OPLSAA force field. The seven residue peptide (Lys-Leu-Val-Phe-Phe-Ala-Glu) A β ₁₆₋₂₂ associated with AD was studied and reported in this paper.

Heterogeneous Hydration of p53/MDM2 Complex

Zuojun Guo, Bo Li, Joachim Dzubiella, Li-Tien Cheng, J. Andrew McCammon, Jianwei Che [Genomics Institute of the Novartis Research Foundation]

J. Chem. Theor. and Comp., **10**, 1302–1313, 2014.

Water-mediated interactions play critical roles in biomolecular recognition processes. Explicit solvent molecular dynamics (MD) simulations and the variational implicit-solvent model (VISM) are used to study those hydration properties during binding for the biologically important p53/MDM2 complex. Unlike simple model solutes, in such a realistic and heterogeneous solute–solvent system with both geometrical and chemical complexity, the local water distribution sensitively depends on nearby amino acid properties and the geometric shape of the protein.

Constant pH Replica Exchange Molecular Dynamics in Explicit Solvent Using Discrete Protonation States: Implementation, Testing, and Validation

Jason M. Swails, Darrin M. York, Adrian E. Roitberg [University of Florida]

J. Chem. Theor. and Comp., **10**, 1341–1352, 2014.

By utilizing Graphics Processing Units, we show that constant pH molecular dynamics simulations (CpHMD) run in Generalized Born (GB) implicit solvent for long time scales can yield poor pKa predictions as a result of sampling unrealistic conformations. To address this shortcoming, we present a method for performing constant pH molecular dynamics simulations (CpHMD) in explicit solvent using a discrete protonation state model. The method involves standard molecular dynamics (MD) being propagated in explicit solvent followed by protonation state changes being attempted in GB implicit solvent at fixed intervals.

Protein Dynamics (Cont'd)

Role of histidine for charge regulation of unstructured peptides at interfaces and in bulk

Anil Kurut[Lund University], João Henriques, Jan Forsman, Marie Skepö, Mikael Lund

Proteins: Stru. Fun. & Bioinf., **82**, 657–667, 2014.

Histidine-rich, unstructured peptides adsorb to charged interfaces such as mineral surfaces and microbial cell membranes. At a molecular level, we investigate the adsorption mechanism as a function of pH, salt, and multivalent ions showing that (1) proton charge fluctuations are—in contrast to the majority of proteins—optimal at neutral pH, promoting electrostatic interactions with anionic surfaces through charge regulation and (2) specific zinc(II)-histidine binding competes with protons and ensures an unusually constant charge distribution over a broad pH interval. In turn, this further enhances surface adsorption.

Molecular Dynamics Simulations Approach for the Characterization of Peptides with Respect to Hydrophobicity

Sven Amrhein, Stefan Alexander Oelmeier, Florian Dismer, Jürgen Hubbuch [Institute of Process Engineering in Life Sciences, KIT]

J. Phys. Chem. B., **118**, 1707–1714, 2014.

It has been shown that MD simulations are a powerful tool to generate knowledge about complex interactions in the field of bioprocess technologies at the atomic level. In this field, one of the most important nonspecific interactions is the hydrophobic interaction, which is still not fully understood after nearly 30 years of research. To date established hydrophobicity scales, which base mostly on proteins' primary structure, are used to estimate the overall hydrophobicity. In this work, free solution molecular dynamics simulations were used to investigate the hydrophobic character of low molecular weight peptides.

Urea Induced Unfolding Dynamics of Flavin Adenine Dinucleotide (FAD): Spectroscopic and Molecular Dynamics Simulation Studies from Femto-Second to Nanosecond Regime

Abhigyan Sengupta, Reman K. Singh, Krishna Gavvala, Raj Kumar Koninti, Arnab Mukherjee, Partha Hazra [Indian Institute of Science Education and Research (IISER)-Pune]

J. Phys. Chem. B., **118**, 1881–1890, 2014.

We investigate the effect of urea in the unfolding dynamics of flavin adenine dinucleotide (FAD), an important enzymatic cofactor, through steady state, time-resolved fluorescence spectroscopic and molecular dynamics (MD) simulation studies. Steady state results indicate the possibility of urea induced unfolding of FAD, inferred from increasing emission intensity of FAD with urea. The TCSPC and up-conversion results suggest that the stack-unstack dynamics of FAD severely gets affected in the presence of urea and leads to an increase in the unstack conformation population from 15% in pure water to 40% in 12 M urea.

Mechanistic Study of the Deamidation Reaction of Glutamine: A Computational Approach

Mohammad A. Halim, Mansour H. Almatarneh, Raymond A. Poirier [Memorial University]

J. Phys. Chem. B., **118**, 2316–2330, 2014.

Glutamine—a popular nutritional supplement, non-toxic amino acid, and an essential interorgan and intercellular ammonia transporter—can destroy the neurons' mitochondria. When glutamine enters (like a Trojan horse) into the mitochondria, in the presence of glutaminase, it reacts with water and yields glutamate and excess ammonia which opens gates in the membrane of the mitochondria and thereby destroys it. The mechanistic details underlying the molecular basis of the catabolic production of excess ammonia remain unclear. In the present paper, both 5-oxoproline-mediated and direct pathways for glutamine deamidation are studied using wave function and density functional theories.

Protein Dynamics (Cont'd)

A New Theoretical Approach to Analyze Complex Processes in Cytoskeleton Proteins

Xin Li , Anatoly B. Kolomeisky [Rice University]

J. Phys. Chem. B., **118**, 2966–2972, 2014.

Cytoskeleton proteins are filament structures that support a large number of important biological processes. These dynamic biopolymers exist in nonequilibrium conditions stimulated by hydrolysis chemical reactions in their monomers. Current theoretical methods provide a comprehensive picture of biochemical and biophysical processes in cytoskeleton proteins. However, the description is only qualitative under biologically relevant conditions because utilized theoretical mean-field models neglect correlations. We develop a new theoretical method to describe dynamic processes in cytoskeleton proteins that takes into account spatial correlations in the chemical composition of these biopolymers.

Hydrogen Bond Dynamics in Intrinsically Disordered Proteins

Nidhi Rawat , Parbati Biswas [University of Delhi]

J. Phys. Chem. B., **118**, 3018–3025, 2014.

Hydrogen bond dynamics is used to investigate the internal motions and structural plasticity of intrinsically disordered (ID) proteins. Group a represent completely disordered proteins, while group b proteins are comprised of regular secondary structures linked by flexible disordered regions. Molecular dynamics simulations of two different groups of ID proteins provide an insight into the hydrogen bond dynamics via the evaluation of the continuous and intermittent time autocorrelation functions. The intermolecular hydrogen bonds between the residues of the ID proteins and water record a short lifetime in both groups of proteins.

Free Energy Calculations

Bringing Clarity to the Prediction of Protein–Ligand Binding Free Energies via “Blurring”

Melek N. Ucisik, Zheng Zheng, John C. Faver, Kenneth M. Merz [University of Florida]

J. Chem. Theor. and Comp., **10**, 1314–1325, 2014.

We present a method to evaluate the free energies of ligand binding utilizing a Monte Carlo estimation of the configuration integrals concomitant with uncertainty quantification. Ensembles for integration are built through systematically perturbing an initial ligand conformation in a rigid binding pocket, which is optimized separately prior to incorporation of the ligand. We call the procedure producing the ensembles “blurring”, and it is carried out using an in-house developed code.

Ligand Binding/Docking

Structural insight into the binding complex: β -arrestin/CCR5 complex

Nejla Stambouli [Military Hospital, Tunis], Mehdi Dridi, Ning-Ning Wei, Asma Jlizi, Abderahmen Bouraoui , Amel Ben Ammar Elgaai

J. Biomol. Stru. and Dyn., 32, 866-875,2014.

The chemokine receptor 5 (CCR5) belongs to the superfamily of serpentine G protein-coupled receptors (GPCRs). The DRY motif (Asp, Arg, Tyr) of the intracellular loop 2 (ICL2), which is highly conserved in the GPCRs has been shown to be essential for the stability of folding of CCR5 and the interaction with β -arrestin. But the molecular mechanism by which it recognizes and interacts with β -arrestin has not been elucidated. In the present study, we described the active state of the β -arrestin structure using normal mode analysis and characterized the binding cleft of CCR5-ICL2 with β -arrestin using SABRE© docking tool and molecular dynamics simulation.

Influence of GTP/GDP and magnesium ion on the solvated structure of the protein FtsZ: a molecular dynamics study

Carla Jamous, Nathalie Basdevant , Tap Ha-Duong [Faculté de Pharmacie – Université Paris Sud]

J. Biomol. Stru. and Dyn., 32, 916-927,2014.

We present here a structural analysis of ten extensive all-atom molecular dynamics simulations of the monomeric protein FtsZ in various binding states. Since the polymerization and GTPase activities of FtsZ depend on the nature of a bound nucleotide as well as on the presence of a magnesium ion, we studied the structural differences between the average conformations of the following five systems: FtsZ-Apo, FtsZ-GTP, FtsZ-GDP, FtsZ-GTP-Mg, and FtsZ-GDP-Mg. The in silico solvated average structure of FtsZ-Apo significantly differs from the crystallographic structure 1W59 of FtsZ which was crystallized in a dimeric form without nucleotide and magnesium.

Effect of ligand binding on the dynamics of trypsin. Comparison of different approaches

Elena Ermakova [Kazan Institute of Biochemistry and Biophysics RAS], Rauf Kurbanov

J. Mol.Graph. and Mod., 49, 99-109, 2014.

The intramolecular signal transduction induced by the binding of ligands to trypsin was investigated by molecular dynamics simulations. Ligand binding changes the residue-residue interaction energies and suppresses the mobility of loops that are in direct contact with the ligand. The reduced mobility of these loops results in the altered flexibility of the nearby loops and thereby transmits the information from ligand binding site to the remote sites. The analysis of the flexibility of all residues confirmed the coupling between loops L1 (185–188) and L2 (221–224) and the residues in the active center.

Ligand Binding / Docking (Cont'd)

Computing Clinically Relevant Binding Free Energies of HIV-1 Protease Inhibitors

David W. Wright, Benjamin A. Hall, Owain A. Kenway, Shantenu Jha, Peter V. Coveney [Rutgers University]

J. Chem. Theor. and Comp., **10**, 1228–1241, 2014.

The use of molecular simulation to estimate the strength of macromolecular binding free energies is becoming increasingly widespread, with goals ranging from lead optimization and enrichment in drug discovery to personalizing or stratifying treatment regimes. In order to realize the potential of such approaches to predict new results, not merely to explain previous experimental findings, it is necessary that the methods used are reliable and accurate, and that their limitations are thoroughly understood. Here, we present a detailed analysis of two of the most popular approximate methods for calculating binding free energies from molecular simulations, molecular mechanics Poisson–Boltzmann surface area and molecular mechanics generalized Born surface area, applied to the nine FDA-approved HIV-1 protease inhibitors.

Kinetic Characterization of Fragment Binding in AmpC β -Lactamase by High-Throughput Molecular Simulations

P. Bisignano, S. Doerr, M. J. Harvey, A. D. Favia, A. Cavalli [Università di Bologna], G. De Fabritiis

J. Chem. Infor. and Mod., **54**, 362–366, 2014.

Small molecules used in fragment-based drug discovery form multiple, promiscuous binding complexes difficult to capture experimentally. Here, we identify such binding poses and their associated energetics and kinetics using molecular dynamics simulations on AmpC β -lactamase. Only one of the crystallographic binding poses was found to be thermodynamically favorable; however, the ligand shows several binding poses within the pocket. This study demonstrates free-binding molecular simulations in the context of fragment-to-lead development and its potential application in drug design.

Specificity of a protein–protein interface: Local dynamics direct substrate recognition of effector caspases

Julian E. Fuchs, Susanne von Grafenstein, Roland G. Huber, Hannes G. Wallnoefer, Klaus R. Liedl [University of Innsbruck]

Proteins: Stru. Fun. & Bioinf., **82**, 546–555, 2014.

Proteases are prototypes of multispecific protein–protein interfaces. Proteases recognize and cleave protein and peptide substrates at a well-defined position in a substrate binding groove and a plethora of experimental techniques provide insights into their substrate recognition. We investigate the caspase family of cysteine proteases playing a key role in programmed cell death and inflammation, turning caspases into interesting drug targets. Specific ligand binding to one particular caspase is difficult to achieve, as substrate specificities of caspase isoforms are highly similar.

Enzyme Catalysis

Assigning the EPR Fine Structure Parameters of the Mn(II) Centers in *Bacillus subtilis* Oxalate Decarboxylase by Site-Directed Mutagenesis and DFT/MM Calculations

Pablo Campomanes, Whitney F. Kellett, Lindsey M. Easthon, Andrew Ozarowski, Karen N. Allen, Alexander Angerhofer, Ursula Rothlisberger, and Nigel G. J. Richards

J. Am. Chem. Soc., 2013, **136**, 2313–2323, 2014.

Oxalate decarboxylase (OxDC) catalyzes the Mn-dependent conversion of the oxalate monoanion into CO₂ and formate. EPR-based strategies for investigating the catalytic mechanism of decarboxylation are complicated by the difficulty of assigning the signals associated with the two Mn(II) centers located in the N- and C-terminal cupin domains of the enzyme. We now report a mutational strategy that has established the assignment of EPR fine structure parameters to each of these Mn(II) centers at pH 8.5.

Are There Really Low-Barrier Hydrogen Bonds in Proteins? The Case of Photoactive Yellow Protein

Marc Nadal-Ferret, Ricard Gelabert, Miquel Moreno, José M. Lluch [Universitat Autònoma de Barcelona]

J. Am. Chem. Soc., 2013, **136**, 3542–3552, 2014.

For a long time, low-barrier hydrogen bonds (LBHBs) have been proposed to exist in many enzymes and to play an important role in their catalytic function, but the proof of their existence has been elusive. The transient formation of an LBHB in a protein system has been detected for the first time using neutron diffraction techniques on a photoactive yellow protein (PYP) crystal in a study published in 2009. By means of electronic structure calculations combined with the solution of the nuclear Schrödinger equation, we analyze here under which conditions an LBHB can exist in PYP, thus leading to a more reasonable and conciliating understanding of the above-mentioned studies.

Design of an interface peptide as new inhibitor of human glucose-6-phosphate dehydrogenase

Cristian Obiol-Pardo, Gema Alcarraz-Vizán, Santiago Díaz-Moralli, Marta Cascante, Jaime Rubio-Martinez [University of Barcelona and Institut de Recerca en Química Teòrica i Computacional (XRQTC)]

J. Mol. Graph. and Mod., **49**, 110–117, 2014.

Glucose-6-phosphate dehydrogenase (G6PDH) is an essential enzyme involved in the first reaction of the oxidative branch of the pentose phosphate pathway (PPP). Recently, G6PDH was suggested as a novel target protein for cancer therapy as one of the final products of the PPP, ribose-5-phosphate, is necessary for nucleic acid synthesis and tumor progression. After analyzing the protein–protein interface of the crystal structure of human G6PDH by means of molecular dynamics simulations, we designed six interface peptides based on the natural sequence of the protein.

Concerted Cyclization of Lanosterol C-Ring and D-Ring Under Human Oxidosqualene Cyclase Catalysis: An ab Initio QM/MM MD Study

Nanhao Chen, Jingwei Zhou, Jiabo Li, Jun Xu, Ruibo Wu [Sun Yat-sen University]

J. Chem. Theor. and Comp., **10**, 1109–1120, 2014.

Human oxidosqualene cyclase (OSC) is one key enzyme in the biosynthesis of cholesterol. It can catalyze the linear-chain 2,3-oxidosqualene to form lanosterol, the tetracyclic (6–6–6–5 members for A–B–C–D rings) cholesterol precursor. It also has been treated as a novel antihyperlipidemia target. In addition, the structural diversity of cyclic terpenes in plants originates from the cyclization of 2,3-oxidosqualene. The enzyme catalytic mechanism is considered to be one of the most complicated ones in nature, and there are a lot of controversies about the mechanism in the past half a century. Herein, state-of-the-art ab initio QM/MM MD simulations are employed to investigate the detailed cyclization mechanism of C-ring and D-ring formation.

Enzyme Catalysis (Cont'd)

Quantum Mechanical/Molecular Mechanical Study of Catalytic Mechanism and Role of Key Residues in Methylation Reactions Catalyzed by Dimethylxanthine Methyltransferase in Caffeine Biosynthesis

Yufei Yue ,Hong Guo [University of Tennessee]

J.Chem. Infor. and Mod. **54**, 593–600, 2014.

The caffeine biosynthetic pathway is of considerable importance for the beverage and pharmaceutical industries which produces two blockbuster products: theobromine and caffeine. The major biochemistry in caffeine biosynthesis starts from the initial substrate of xanthosine and ends with the final product caffeine, with theobromine serving as an intermediate. The key enzyme, S-adenosyl-L-methionine (SAM) dependent 3,7-dimethyl-xanthine methyltransferase (DXMT), catalyzes two important methyl transfer steps in caffeine biosynthesis: (1) methylation of N3 of 7-methylxanthine (7mX) to form theobromine (Tb); (2) methylation of N1 of theobromine to form caffeine (Cf).

Reaction Mechanism of Homoprotocatechuate 2,3-Dioxygenase with 4-Nitrocatechol: Implications for the Role of Substrate

Geng Dong , Wenzhen Lai [Renmin University of China]

J. Phys. Chem. B., **118**, 1791–1798, 2014.

The reaction mechanism of the dioxygen activation by homoprotocatechuate 2,3-dioxygenase (HPCD) with the substrate 4-nitrocatechol was investigated by quantum mechanical/molecular mechanical calculations. Our results demonstrated that the experimentally determined side-on iron–oxygen complex in crystallo is a semiquinone substrate radical (SQ•)–FeIII–hydroperoxo species, which could not act as the reactive species. In fact, the FeIII–superoxo species with a hydrogen bond between His200 and the proximal oxygen is the reactive oxygen species. The second-sphere His200 residue was found to play an important role in manipulating the orientation of the superoxide in the Fe–O₂ adduct for the further reaction.

Catalytic Mechanism of Histone Acetyltransferase p300: From the Proton Transfer to Acetylation Reaction

Xinlei Zhang, Sisheng Ouyang, Xiangqian Kong, Zhongjie Liang, Junyan Lu, Kongkai Zhu, Dan Zhao, Mingyue Zheng, Hualiang Jiang, Xin Liu, Ronen Marmorstein, Cheng Luo [Chinese Academy of Sciences]

J. Phys. Chem. B., **118**, 2009–2019, 2014.

In this study, a combined computational strategy consisting of molecular modeling, molecular dynamic (MD) simulation, and quantum mechanics/molecular mechanics (QM/MM) simulation was applied to elucidate these important issues. An initial p300/H3/Ac-CoA complex structure was modeled and optimized using a 100 ns MD simulation. Residues that play important roles in substrate binding and the acetylation reaction were comprehensively investigated. For the first time, these studies reveal a plausible PT scheme consisting of Y1394, D1507, and a conserved crystallographic water molecule, with all components of the scheme being stable during the MD simulation and the energy barrier low for PT to occur.

Enzyme Catalysis (Cont'd)

Effect of Protein Environment within Cytochrome P450cam Evaluated Using a Polarizable-Embedding QM/MM Method

Nandun M. Thellamurege , Hajime Hirao [Nanyang Technological University]

J. Phys. Chem. B., **118**, 2084–2092, 2014.

Metalloenzymes accommodate cofactors and substrates in their active sites, thereby exerting powerful catalytic effects. To address this issue computationally, here we used mechanical-embedding (ME), electronic-embedding (EE), and polarizable-embedding (PE) hybrid quantum mechanics and molecular mechanics (QM/MM) methods and performed an energy decomposition analysis (EDA) of the nonbonding protein environmental effect in the “compound I” intermediate state of cytochrome P450cam. The B3LYP and AMBER99/QP302 methods were used to deal with the QM and MM subsystems, respectively, and the nonbonding interaction energy between these subsystems was decomposed into electrostatic, van der Waals, and polarization contributions.

Experimental and Modeling Studies of an Unusual Water-Filled Pore Structure with Possible Mechanistic Implications in Family 48 Cellulases

Mo Chen, Maxim Kostylev, Yannick J. Bomble, Michael F. Crowley, Michael E. Himmel, David B. Wilson, John W. Brady [Cornell University]

J. Phys. Chem. B., **118**, 2306–2315, 2014.

Molecular dynamics simulations were used to study the possible catalytic role of an unusual conserved water-filled pore structure in the family 48 cellulase enzyme Cel48A from *Thermobifida fusca*. It was hypothesized that this pore serves as the pathway for the water molecules consumed in the hydrolysis catalyzed by the enzyme to reach the active site in a continuous stream to participate in the processive reactions. Theoretical mutants of this enzyme were created in which all of the residues lining the pore were made hydrophobic, which had the effect in molecular dynamics simulations of emptying the pore of water molecules and preventing any from passing through the pore on the simulation time scale.

Protein-Protein Interactions

NetCoffee: a fast and accurate global alignment approach to identify functionally conserved proteins in multiple networks

Jialu Hu [Freie Universität Berlin], Birte Kehr, Knut Reinert

Bioinformatics. **30**, 540–548, 2014.

Owing to recent advancements in high-throughput technologies, protein–protein interaction networks of more and more species become available in public databases. The question of how to identify functionally conserved proteins across species attracts a lot of attention in computational biology. *Network alignments* provide a systematic way to solve this problem. However, most existing alignment tools encounter limitations in tackling this problem. Therefore, the demand for faster and more efficient alignment tools is growing. We present a fast and accurate algorithm, *NetCoffee*, which allows to find a global alignment of multiple protein–protein interaction networks.

Protein-Protein Interactions (Cont'd)

Molecular Dynamics Studies of the Protein-Protein Interactions in Inhibitor of κ B Kinase- β

Michael R. Jones, Cong Liu, Angela K. Wilson [University of North Texas]

J.Chem. Infor. and Mod. **54**, 562–572, 2014.

Activation of the inhibitor of κ B kinase subunit β (IKK β) oligomer initiates a cascade that results in the translocation of transcription factors involved in mediating immune responses. Dimerization of IKK β is required for its activation. Coarse-grained and atomistic molecular dynamics simulations were used to investigate the conformation-activity and structure-activity relationships within the oligomer assembly of IKK β that are impacted upon activation, mutation, and binding of ATP.

Membrane Proteins and Lipid Peptide Interactions

Protein and Lipid Interactions Driving Molecular Mechanisms of in meso Crystallization

Niklaus Johnner, Sayan Mondal, Giulia Morra, Martin Caffrey, Harel Weinstein, George Khelashvili [Weill Cornell Medical College of Cornell University]

J. Am. Chem. Soc., 2013, **136**, 3271–3284, 2014.

The recent advances in the in meso crystallization technique for the structural characterization of G-protein coupled receptor (GPCR) proteins have established the usefulness of the lipidic-cubic phases (LCPs) in the field of crystallography of membrane proteins. It is surprising that despite the success of the approach, the molecular mechanisms of the in meso method are still not well understood. Therefore, the approach must rely on extensive screening for a suitable protein construct, for host and additive lipids, and for the appropriate precipitants and temperature. To shed light on the in meso crystallization mechanisms.

Atomistic simulation studies of the α/β -glucoside and galactoside in anhydrous bilayers: effect of the anomeric and epimeric configurations

Sara Ahmadi, Vijayan Manickam Achari, HockSeng Nguan, Rauzah Hashim [University of Malaya]

J. Mol.Mod., **20**, 2165, 2014.

Fully atomistic molecular dynamics simulation studies of thermotropic bilayers were performed using a set of glycosides namely n-octyl- β -D-glucopyranoside (β -C8Glc), n-octyl- α -D-glucopyranoside (α -C8Glc), n-octyl- β -D-galactopyranoside (β -C8Gal), and n-octyl- α -D-galactopyranoside (α -C8Gal) to investigate the stereochemical relationship of the epimeric/anomeric quartet liner glycolipids with the same octyl chain group. The results showed that, the anomeric stereochemistry or the axial/equatorial orientation of C1–O1 (α/β) is an important factor controlling the area and *d*-spacing of glycolipid bilayer systems in the thermotropic phase.

Supervised Molecular Dynamics (SuMD) as a Helpful Tool To Depict GPCR–Ligand Recognition Pathway in a Nanosecond Time Scale

Davide Sabbadin, Stefano Moro [Università di Padova]

J.Chem. Infor. and Mod. **54**, 372–376, 2014.

Supervised MD (SuMD) is a computational method that allows the exploration of ligand–receptor recognition pathway investigations in a nanosecond (ns) time scale. It consists of the incorporation of a tabu-like supervision algorithm on the ligand–receptor approaching distance into a classic molecular dynamics (MD) simulation technique. In addition to speeding up the acquisition of the ligand–receptor trajectory, this implementation facilitates the characterization of multiple binding events (such as meta-binding, allosteric, and orthosteric sites) by taking advantage of the all-atom MD simulations accuracy of a GPCR–ligand complex embedded into explicit lipid–water environment.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Including Explicit Water Molecules as Part of the Protein Structure in MM/PBSA Calculations

Yong-Liang Zhu [Elan Pharmaceutical], Paul Beroza, Dean R. Artis

J.Chem. Infor. and Mod. **54**, 462–469, 2014.

Water is the natural medium of molecules in the cell and plays an important role in protein structure, function and interaction with small molecule ligands. However, the widely used molecular mechanics Poisson–Boltzmann surface area (MM/PBSA) method for binding energy calculation does not explicitly take account of water molecules that mediate key protein–ligand interactions. We have developed a protocol to include water molecules that mediate ligand–protein interactions as part of the protein structure in calculation of MM/PBSA binding energies (a method we refer to as water–MM/PBSA) for a series of JNK3 kinase inhibitors.

Steered Molecular Dynamics Simulations for Studying Protein–Ligand Interaction in Cyclin-Dependent Kinase 5

Jagdish Suresh Patel, Anna Berteotti, Simone Ronsisvalle, Walter Rocchia, Andrea Cavalli [University of Bologna]

J.Chem. Infor. and Mod. **54**, 470–480, 2014.

In this study, we applied steered molecular dynamics (SMD) simulations to investigate the unbinding mechanism of nine inhibitors of the enzyme cyclin-dependent kinase 5 (CDK5). The study had two major objectives: (i) to create a correlation between the unbinding force profiles and the inhibition activities of these compounds expressed as IC₅₀ values; (ii) to investigate the unbinding mechanism and to reveal atomistic insights, which could help identify accessory binding sites and transient interactions. Overall, we carried out 1.35 μ s of cumulative SMD simulations.

Molecular Dynamics Simulations of the Adenosine A2a Receptor in POPC and POPE Lipid Bilayers: Effects of Membrane on Protein Behavior

Hui Wen Ng, Charles A. Laughton, Stephen W. Doughty [University of Nottingham Malaysia Campus]

J.Chem. Infor. and Mod. **54**, 573–581, 2014.

Analysis of 300 ns (ns) molecular dynamics (MD) simulations of an adenosine A2a receptor (A2a AR) model, conducted in triplicate, in 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) and 1-palmitoyl-2-oleoylphosphatidylethanolamine (POPE) bilayers reveals significantly different protein dynamical behavior. Principal component analysis (PCA) shows that the dissimilarities stem from interhelical rather than intrahelical motions. The difference in the hydrophobic thicknesses of these simulated lipid bilayers is potentially a significant reason for the observed difference in results.

A Microscopic View of Phospholipid Insertion into Biological Membranes

Josh V. Vermaas, Emad Tajkhorshid [University of Illinois at Urbana–Champaign]

J. Phys. Chem. B., **118**, 1754–1764, 2014.

Through a comparative study, we assess the difference in insertion rate of a free phospholipid into an HMMM as well as into a conventional phospholipid bilayer and develop a detailed mechanistic model of free phospholipid insertion into biological membranes. The mechanistic insertion model shows that successful irreversible association of the free phospholipid to the membrane interface, which results in its insertion, is the rate-limiting step. Association is followed by independent, sequential insertion of the acyl tails of the free phospholipid into the membrane, with splayed acyl tail intermediates.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Alzheimer's A β 10–40 Peptide Binds and Penetrates DMPC Bilayer: An Isobaric–Isothermal Replica Exchange Molecular Dynamics Study

Christopher Lockhart , Dmitri K. Klimov [George Mason University]

J. Phys. Chem. B., **118**, 2638–2648, 2014.

Using all-atom explicit solvent model and isobaric–isothermal replica exchange molecular dynamics, we studied binding of A β 10–40 monomers to zwitterionic DMPC bilayer. Our simulations suggest three main conclusions. First, binding of A β 10–40 monomer to the DMPC bilayer causes dramatic structural transition in the peptide resulting in the formation of stable helical structure in the C-terminal. In addition, binding to the lipid bilayer induces the formation of intrapeptide Asp23–Lys28 salt bridge. We argue that the emergence of helix is the consequence of hidden helix propensity harbored in the A β 10–40 C-terminal.

Translocation Thermodynamics of Linear and Cyclic Nonaarginine into Model DPPC Bilayer via Coarse-Grained Molecular Dynamics Simulation: Implications of Pore Formation and Nonadditivity

Yuan Hu, Xiaorong Liu, Sudipta Kumar Sinha, Sandeep Patel [University of Delaware]

J. Phys. Chem. B., **118**, 2670–2682, 2014.

Structural mechanisms and underlying thermodynamic determinants of efficient internalization of charged cationic peptides (cell-penetrating peptides, CPPs) such as TAT, polyarginine, and their variants, into cells, cellular constructs, and model membrane/lipid bilayers (large and giant unilamellar or multilamellar vesicles) continue to garner significant attention. Two widely held views on the translocation mechanism center on endocytotic and nonendocytotic (diffusive) processes. Espousing the view of a purely diffusive internalization process (supported by recent experimental evidence, [Säälik, P.; et al. *J. Controlled Release* 2011, 153, 117–125]), we consider the underlying free energetics of the translocation of a nonaarginine peptide (Arg9) into a model DPPC bilayer.

Protein Folding

Botulinum neurotoxin: unique folding of enzyme domain of the most-poisonous poison

Raj Kumar, Roshan V. Kukreja, Li Li, Artem Zhmurov, Olga Kononova, Shuowei Cai, Syed A. Ahmed, Valeri Barsegov , Bal Ram Singh [University of Massachusetts]

J. Biomol. Stru. and Dyn., **32**, 804-815, 2014.

Botulinum neurotoxin (BoNT), the most toxic substance known to mankind, is the first example of the fully active molten globule state. To understand its folding mechanism, we performed urea denaturation experiments and theoretical modeling using BoNT serotype A (BoNT/A). We found that the extent of BoNT/A denaturation from the native state (N) shows a nonmonotonic dependence on urea concentration indicating a unique multistep denaturation process, N $\rightarrow$ I1 I2 U, with two intermediate states I1 and I2. BoNT/A loses almost all its secondary structure in 3.75 M urea (I1), yet it displays a native-like secondary structure in 5 M urea (I2).

Protein Folding (Cont'd)

Nanomechanics of β -rich proteins related to neuronal disorders studied by AFM, all-atom and coarse-grained MD methods

Karolina Mikulska, Janusz Strzelecki, Wiesław Nowak
[Nicolaus Copernicus University]

J. Mol.Mod., **20**, 2144, 2014.

Computer simulations of protein unfolding substantially help to interpret force-extension curves measured in single-molecule atomic force microscope (AFM) experiments. Standard all-atom (AA) molecular dynamics simulations (MD) give a good qualitative mechanical unfolding picture but predict values too large for the maximum AFM forces with the common pulling speeds adopted here. Fine tuned coarse-grain MD computations (CG MD) offer quantitative agreement with experimental forces. In this paper we address an important methodological aspect of MD modeling, namely the impact of numerical noise generated by random assignments of bead velocities on maximum forces ($F_{\max}$) calculated within the CG MD approach.

The maturation of HIV-1 protease precursor studied by discrete molecular dynamics

Sachie Kimura, Martina Caldarini, Ricardo A. Broglia, Nikolay V. Dokholyan, Guido Tiana [Università degli Studi di Milano]

Proteins: Stru. Fun. & Bioinf., **82**, 633-639, 2014.

The equilibrium properties of a HIV-1-protease precursor are studied by means of an efficient molecular dynamics scheme, which allows for the simulation of the folding of the protein monomers and their dimerization into an active form and compare them with those of the mature protein. The results of the model provide, with atomic detail, an overall account of several experimental findings, including the NMR conformation of the mature dimer, the calorimetric properties of the system, the effects of the precursor tail on the dimerization constant, the secondary chemical shifts of the monomer, and the paramagnetic relaxation enhancement data associated with the conformations of the precursor.

Protein-Nucleic acid Interactions

A penalized Bayesian approach to predicting sparse protein-DNA binding landscapes

Matthew Levinson, Qing Zhou [University of California]

Bioinformatics. **30**, 636-643, 2014.

Cellular processes are controlled, directly or indirectly, by the binding of hundreds of different DNA binding factors (DBFs) to the genome. One key to deeper understanding of the cell is discovering where, when and how strongly these DBFs bind to the DNA sequence. We develop SparScape, a penalized Bayesian method for identifying DBFs active in the considered regions and predicting a joint probabilistic binding landscape. Using a sparsity-inducing penalization, SparScape is able to select a small subset of DBFs with enriched BSs in a set of DNA sequences from a much larger candidate set. This substantially reduces the false positives in prediction of BSs.

Protein - Nucleic Acid Interactions (Cont'd)

MD and NMR Analyses of Choline and TMA Binding to Duplex DNA: On the Origins of Aberrant Sequence-Dependent Stability by Alkyl Cations in Aqueous and Water-Free Solvents

Guillem Portella, Markus W. Germann, Nicholas V. Hud [Institute of Technology, Atlanta], and Modesto Orozco

J. Am. Chem. Soc., 2013, **136**, 3075–3086, 2014.

It has been known for decades that alkylammonium ions, such as tetramethyl ammonium (TMA), alter the usual correlation between DNA GC-content and duplex stability. In some cases it is even possible for an AT-rich duplex to be more stable than a GC-rich duplex of the same length. There has been much speculation regarding the origin of this aberration in sequence-dependent DNA duplex stability, but no clear resolution. Using a combination of molecular dynamics simulations and NMR spectroscopy we demonstrate that choline and TMA are preferentially localized in the minor groove of DNA duplexes at A•T base pairs and these same ions show less pronounced localization in the major groove compared to what has been demonstrated for alkali and alkali earth metal ions.

Non-specificity and synergy at the binding site of the carboplatin-induced DNA adduct via molecular dynamics simulations of the MutSα–DNA recognition complex

Lacramioara Negureanu ,Freddie R. Salsbury Jr [Wake Forest University]

J. Biomol. Stru. and Dyn., 32, 969-992,2014.

MutSα is the most abundant mismatch-binding factor of human DNA mismatch repair (MMR) proteins. MMR maintains genetic stability by recognizing and repairing DNA defects. Failure to accomplish their function may lead to cancer. In addition, MutSα recognizes at least some types of DNA damage making it a target for anticancer agents. Here, complementing scarce experimental data, we report unique hydrogen-bonding motifs associated with the recognition of the carboplatin induced DNA damage by MutSα. These data predict that carboplatin and cisplatin induced damaging DNA adducts are recognized by MutSα in a similar manner.

Steered molecular dynamics identifies critical residues of the Nodamura virus B2 suppressor of RNAi

William J. Allen [Virginia Tech, Blacksburg], Michael R. Wiley, Kevin M. Myles, Zach N. Adelman, David R. Bevan

J. Mol.Mod., **20**, 2092, 2014.

Nearly all RNA viruses produce double-stranded RNA (dsRNA) during their replication cycles—an important pathogen-associated molecular pattern recognized by the RNA interference (RNAi) pathway in invertebrates and plants. Nodamura virus (NoV) encodes a suppressor of RNA silencing termed B2, which binds to dsRNA and prevents the initiation of RNAi as well as the loading of silencing complexes. Using the published crystal structure of NoV-B2, we performed a series of molecular dynamics (MD) simulations to determine the relative electrostatic and van der Waals contributions of various residues in binding dsRNA, identifying four novel potential interactors: R56, E48, P68 and R69.

Protein - Nucleic Acid Interactions (Cont'd)

UV-vis absorption spectrum of a novel Ru(II) complex intercalated in DNA: [Ru(2,2'-bipy)(dppz)(2,2'-ArPy)]⁺

Agisilaos Chantzis [Université de Lorraine Nancy], Thibaut Very, Stéphane Despax, Jean-Thomas Issenhuth, Alex Boeglin, Pascal Hébraud, Michel Pfeffer, Antonio Monari, Xavier Assfeld

J. Mol.Mod., **20**, 2082, 2014.

The synthesis of a new Ru(II) complex is reported. Its absorption spectrum when interacting with DNA in water was calculated at the hybrid quantum mechanics molecular mechanics level of theory and compared with experimental data. The vertical transitions were computed using time-dependent density functional theory in the linear response approximation. The complex and its environment were treated at the quantum mechanical and molecular mechanical levels, respectively. The effects of the environment were investigated in detail and conveniently classified into electrostatic and polarization effects.

Hydrophobic Organic Linkers in the Self-Assembly of Small Molecule-DNA Hybrid Dimers: A Computational-Experimental Study of the Role of Linkage Direction in Product Distributions and Stabilities

Ilyas Yildirim, Ibrahim Eryazici, SonBinh T. Nguyen [Northwestern University], George C. Schatz

J. Phys. Chem. B., **118**, 2366–2376 7, 2014.

Detailed computational and experimental studies reveal the crucial role that hydrophobic interactions play in the self-assembly of small molecule-DNA hybrids (SMDHs) into cyclic nanostructures. In aqueous environments, the distribution of the cyclic structures (dimers or higher-order structures) greatly depends on how well the hydrophobic surfaces of the organic cores in these nanostructures are minimized. Specifically, when the cores are attached to the 3'-ends of the DNA component strands, they can insert into the minor groove of the duplex that forms upon self-assembly, favoring the formation of cyclic dimers.

Nucleic Acids

RNASurface: fast and accurate detection of locally optimal potentially structured RNA segments

Ruslan A. Soldatov [Moscow State University], Svetlana V. Vinogradova, Andrey A. Mironov

Bioinformatics. **30**, 457-463, 2014.

Existing programs scan genomes with a fixed window by efficiently constructing a matrix of RNA minimum free energies. A wide range of lengths of structured RNAs necessitates the use of many different window lengths that substantially increases the output size and computational efforts. In this article, we present an algorithm RNASurface to efficiently scan genomes by constructing a matrix of significance of RNA secondary structures and to identify all locally optimal structured RNA segments up to a predefined size. RNASurface significantly improves precision of identification of known ncRNA in *Bacillus subtilis*.

Nucleic Acids (Cont'd)

Molecular structure differences between the antiviral Nucleoside Analogue 5-iodo-2'-deoxyuridine and the natural nucleoside 2'-deoxythymidine using MP2 and DFT methods: conformational analysis, crystal simulations, DNA pairs and possible behaviour

M. Alcolea Palafox [Universidad Complutense]

J. Biomol. Stru. and Dyn., 32, 337-350, 2014.

5-Iodo-2'-deoxyuridine Nucleoside Analogue (IUdR) was the first selective antiviral nucleoside against herpes simplex virus type 1 and 2, and it was also a meaningful anticancer drug. Within a full study of this drug and its possible behaviour, previously, a comprehensive theoretical conformational analysis by MP2 and B3LYP was carried out, and all the possible stable structures were determined with full relaxation of all geometrical parameters. The search located 45 stable structures, and in all them, the whole conformational parameters (ϕ , ψ , χ , ω , θ , τ , ρ , σ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , λ , γ , δ , ϵ , κ , ι , $\jmath$, κ , λ , μ , ν , ξ , η , ζ , $\lambda</$

3D-dynamic representation of DNA sequences

Piotr Wąż [Medical University of Gdańsk], Dorota Bielińska-Wąż

J. Mol.Mod., **20**, 2141, 2014.

A new 3D graphical representation of DNA sequences is introduced. This representation is called 3D-dynamic representation. It is a generalization of the 2D-dynamic dynamic representation. The sequences are represented by sets of “material points” in the 3D space. The resulting 3D-dynamic graphs are treated as rigid bodies. The descriptors characterizing the graphs are analogous to the ones used in the classical dynamics. The classification diagrams derived from this representation are presented and discussed.

The influence of anharmonic and solvent effects on the theoretical vibrational spectra of the guanine–cytosine base pairs in Watson–Crick and Hoogsteen configurations

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Research and Development of Isotopic and Molecular
Technologies]

J. Mol.Mod., **20**, 2113, 2014.

The theoretical IR and Raman spectra of the guanine–cytosine DNA base pairs in Watson–Crick and Hoogsteen configurations were computed using DFT method with M06-2X meta-hybrid GGA exchange–correlation functional, including the anharmonic corrections and solvent effects. The results for harmonic frequencies and their anharmonic corrections were compared with our previously calculated values obtained with the B3PW91 hybrid GGA functional. Significant differences were obtained for the anharmonic corrections calculated with the two different DFT functionals, especially for the stretching modes, while the corresponding harmonic frequencies did not differ considerably.

Probing the Conical Intersection Dynamics of the RNA Base Uracil by UV-Pump Stimulated-Raman-Probe Signals; Ab Initio Simulations

Benjamin P. Fingerhut, Konstantin E. Dorfman, Shaul Mukamel [University of California]

J. Chem. Theor. and Comp, **10**, 1172–1188, 2014.

Nonadiabatic electron and nuclear dynamics of photoexcited molecules involving conical intersections is of fundamental importance in many reactions such as the self-protection mechanism of DNA and RNA bases against UV irradiation. Nonlinear vibrational spectroscopy can provide an ultrafast sensitive probe for these processes. We employ a simulation protocol that combines nonadiabatic on-the-fly molecular dynamics with a mode-tracking algorithm for the simulation of femtosecond stimulated Raman spectroscopy (SRS) signals of the high frequency C-H- and N-H-stretch vibrations of the photoexcited RNA base uracil.

Nucleic Acids (Cont'd)

Tertiary Structure Prediction of RNA–RNA Complexes Using a Secondary Structure and Fragment-Based Method

Satoshi Yamasaki [National Institute of Advanced Industrial Science and Technology (AIST)], Takatsugu Hirokawa, Kiyoshi Asai, Kazuhiko Fukui

J.Chem. Infor. and Mod. **54**, 672–682, 2014.

A method has been developed for predicting the tertiary structures of RNA–RNA complex structures using secondary structure information and a fragment assembly algorithm. The linker base pair and secondary structure potential derived from the secondary structure information are particularly useful for prediction. Application of this method to several kinds of RNA–RNA complex structures, including kissing loops, hammerhead ribozymes, and other functional RNAs, produced promising results. Use of the secondary structure potential effectively restrained the conformational search space, leading to successful prediction of kissing loop structures, which mainly consist of common structural elements.

Surfaces, Catalysts, and Materials Subjects

Different Interfacial Behaviors of Peptides Chemically Immobilized on Surfaces with Different Linker Lengths and via Different Termini

Xiaofeng Han, Yuwei Liu, Fu-Gen Wu, Joshua Jansensky, Taehoon Kim, Zunliang Wang, Charles L. Brooks, III, Jianfeng Wu, Chuanwu Xi, Charlene M. Mello, Zhan Chen

J. Phys. Chem. B., **118**, 2904–2912, 2014.

In this study, sum frequency generation (SFG) vibrational spectroscopy was applied to investigate such structures of peptides immobilized on self-assembled monolayers (SAMs). Here cysteine-modified antimicrobial peptide cecropin P1 (CP1) was chemically immobilized onto SAM with a maleimide terminal group. Two important characteristics, length of the poly(ethylene glycol) (PEG) segment in the SAM and location of the cysteine residue in the peptide, were examined using SFG spectroscopy to determine the effect of each on surface immobilization as well as peptide secondary structure and its orientation in the immobilized state

2. METHODOLOGY

Quantitative Structure-Activity Relations

Assessment of Machine Learning Reliability Methods for Quantifying the Applicability Domain of QSAR Regression Models

Marko Toplak, Rok Močnik, Matija Polajnar, Zoran Bosnić, Lars Carlsson, Catrin Hasselgren, Janez Demšar, Scott Boyer, Blaž Zupan [University of Ljubljana], Jonna Stålring

J.Chem. Infor. and Mod. **54**, 431–441, 2014.

The vastness of chemical space and the relatively small coverage by experimental data recording molecular properties require us to identify subspaces, or domains, for which we can confidently apply QSAR models. The prediction of QSAR models in these domains is reliable, and potential subsequent investigations of such compounds would find that the predictions closely match the experimental values. Standard approaches in QSAR assume that predictions are more reliable for compounds that are “similar” to those in subspaces with denser experimental data. Here, we report on a study of an alternative set of techniques recently proposed in the machine learning community.

Quantitative Structure-Activity Relations (Cont'd)

Application of Quantitative Structure-Activity Relationship Models of 5-HT1A Receptor Binding to Virtual Screening Identifies Novel and Potent 5-HT1A Ligands

Man Luo, Xiang Simon Wang, Bryan L. Roth, Alexander Golbraikh, Alexander Tropsha [Howard University]

J.Chem. Infor. and Mod. **54**, 634–647, 2014.

The 5-hydroxytryptamine 1A (5-HT1A) serotonin receptor has been an attractive target for treating mood and anxiety disorders such as schizophrenia. We have developed binary classification quantitative structure-activity relationship (QSAR) models of 5-HT1A receptor binding activity using data retrieved from the PDSP Ki database. The prediction accuracy of these models was estimated by external 5-fold cross-validation as well as using an additional validation set comprising 66 structurally distinct compounds from the World of Molecular Bioactivity database.

Template CoMFA: The 3D-QSAR Grail?

Richard D. Cramer [Tripos DE], Bernd Wendt

J.Chem. Infor. and Mod. **54**, 660–671, 2014.

Template CoMFA, a novel alignment methodology for training or test set structures in 3D-QSAR, is introduced. Its two most significant advantages are its complete automation and its ability to derive a single combined model from multiple structural series affecting a biological target. Its only two inputs are one or more “template” structures having 3D coordinates that share some Cartesian space, as may result from X-ray crystallography or pharmacophoric hypothesis, and one or more connectivity-only SAR tables associated with a common target.

Molecular Dynamics

Explicit proton transfer in classical molecular dynamics simulations

Maarten G. Wolf, Gerrit Groenhof [University of Jyväskylä]

J. Comp. Chem., **35**, 657–671, 2014.

We present Hydrogen Dynamics (HYDYN), a method that allows explicit proton transfer in classical force field molecular dynamics simulations at thermodynamic equilibrium. HYDYN reproduces the characteristic properties of the excess proton in water, from the special pair dance, to the continuous fluctuation between the limiting Eigen and Zundel complexes, and the water reorientation beyond the first solvation layer.

A computational model of the glycine tautomerization reaction in aqueous solution

Santiago Tolosa [Universidad de Extremadura], Antonio Hidalgo, Jorge A. Sansón

J. Mol.Mod., **20**, 2147, 2014.

A theoretical study of the internal proton transfer reaction of glycine (Gly) in aqueous solution was performed by means of steered molecular dynamics (SMD) simulation with solute-solvent interaction potentials derived from AMBER van der Waals parameters and QM/MM electrostatic charges in solution. Thermodynamic calculations and the analysis of the solvation structure, dynamic properties, and vibrational spectra associated with the species involved in the tautomerization process were performed.

Molecular Dynamics (Cont'd)

Water-mediated potassium acetate intercalation in kaolinite as revealed by molecular simulation

Zoltán Ható, Éva Makó, Tamás Kristóf [University of Pannonia]

J. Mol.Mod., **20**, 2140, 2014.

Molecular simulations are suitable tools to study the adsorption and intercalation of molecules in clays. In this work, a recently proposed thermodynamically consistent force field for inorganic compounds (INTERFACE, Heinz H, Lin TJ, Mishra RK, Emami FS (2013) *Langmuir* 29:1754–1765), which enables accurate simulations of inorganic–organic interfaces, was tested for a two-sheet type clay mineral. All-atom *NpT* molecular dynamics simulations were used to describe the characteristics (basal spacing, loading, molecular orientation) of some intercalate complexes of kaolinite with potassium acetate and the results were compared with the available experimental data.

Monte Carlo

A Comparison of Advanced Monte Carlo Methods for Open Systems: CFCMC vs CBMC

Ariana Torres-Knoop, Sayee Prasaad Balaji, Thijs J. H. Vlugt, David Dubbeldam [University of Amsterdam]

J. Chem. Theor. and Comp, **10**, 942–952, 2014.

Two state-of-the-art simulation methods for computing adsorption properties in porous materials like zeolites and metal–organic frameworks are compared: the configurational bias Monte Carlo (CBMC) method and the recently proposed continuous fractional component Monte Carlo (CFCMC) method. We show that CFCMC is a very significant improvement over CBMC, and we can recommend it as our preferred method of choice. It is faster, more reliable, and (in contrast to CBMC) provides insight on whether or not the results are properly equilibrated.

Free Energy Perturbation

Computation of Standard Binding Free Energies of Polar and Charged Ligands to the Glutamate Receptor GluA2

Germano Heinzelmann, Po-Chia Chen, Serdar Kuyucak [University of Sydney]

J. Phys. Chem. B., **118**, 1813–18247, 2014.

In this study, we use the free energy perturbation (FEP) method with restraints to calculate the standard binding free energy of five ligands (ACPA, AMPA, CNQX, DNQX, and glutamate) to the glutamate receptor GluA2, which plays an essential role in synaptic transmission. To deal with the convergence problem in FEP calculations with charged ligands, we use a protocol where the ligand is coupled in the binding site while it is decoupled in bulk solution simultaneously. The contributions from the conformational, rotational, and translational entropies to the standard binding free energy are determined by applying/releasing respective restraints to the ligand in bulk/binding site.

QM and QM/MM

Intermolecular CH $\cdots$ O/N H-bonds in the biologically important pairs of natural nucleobases: a thorough quantum-chemical study

Ol'ha O. Brovarets', Yevgen P. Yurenko, Dmytro M. Hovorun [National Academy of Sciences of Ukraine]

J. Biomol. Stru. and Dyn., 32, 993-1022, 2014.

This study aims to cast light on the physico-chemical nature and energetic of the non-conventional CH $\cdots$ O/N H-bonds in the biologically important natural nucleobase pairs using a comprehensive quantum-chemical approach. As a whole, the 36 biologically important pairs, involving canonical and rare tautomers of nucleobases, were studied by means of all available up-to-date state-of-the-art quantum-chemical techniques along with quantum theory "Atoms in molecules" (QTAIM), Natural Bond Orbital (NBO) analysis, Grunenberg's compliance constants theory, geometrical and vibrational analyses to identify the CH $\cdots$ O/N interactions, reveal their physico-chemical nature and estimate their strengths as well as contribution to the overall base-pairs stability.

Is the DPT tautomerization of the long A·G Watson–Crick DNA base mispair a source of the adenine and guanine mutagenic tautomers? A QM and QTAIM response to the biologically important question

Ol'ha O. Brovarets, Roman O. Zhurakivsky, Dmytro M. Hovorun [National Academy of Sciences of Ukraine]

J. Comp. Chem., 35, 451–466, 2014.

Herein, we first address the question posed in the title by establishing the tautomerization trajectory *via* the double proton transfer of the adenine·guanine (A·G) DNA base mispair formed by the canonical tautomers of the A and G bases into the A*·G* DNA base mispair, involving mutagenic tautomers, with the use of the quantum-mechanical calculations and quantum theory of atoms in molecules (QTAIM). It was revealed that the A·G base mispair is stabilized by the N6H $\cdots$ O6 (5.68) and N1H $\cdots$ N1 (6.51) hydrogen bonds (H-bonds) and the N2H $\cdots$ HC2 dihydrogen bond (DH-bond) (0.68 kcal·mol $^{-1}$), whereas the A*·G* base mispair—by the O6H $\cdots$ N6 (10.88), N1H $\cdots$ N1 (7.01) and C2H $\cdots$ N2 H-bonds (0.42 kcal·mol $^{-1}$).

Code interoperability and standard data formats in quantum chemistry and quantum dynamics: The Q5/D5Cost data model

Elda Rossi, Stefano Evangelisti, Antonio Laganà, Antonio Monari, Sergio Rampino, Marco Verdicchio, Kim K. Baldrige, Gian Luigi Bendazzoli, Stefano Borini, Renzo Cimiraglia, Celestino Angeli, Peter Kallay, Hans P. Lüthi [ETH Zürich], Kenneth Ruud, José Sanchez-Marin, Anthony Scemama, Peter G. Szalay and Attila Tajti

J. Comp. Chem., 35, 611–621, 2014.

Code interoperability and the search for domain-specific standard data formats represent critical issues in many areas of computational science. The advent of novel computing infrastructures such as computational grids and clouds make these issues even more urgent. The design and implementation of a common data format for quantum chemistry (QC) and quantum dynamics (QD) computer programs is discussed with reference to the research performed in the course of two Collaboration in Science and Technology Actions. The specific data models adopted, Q5Cost and D5Cost, are shown to work for a number of interoperating codes, regardless of the type and amount of information (small or large datasets) to be exchanged.

QM and QM/MM (Cont'd)

Quantum Chemical Calculations Using Accelerators: Migrating Matrix Operations to the NVIDIA Kepler GPU and the Intel Xeon Phi

Sarom S. Leang, Alistair P. Rendell, Mark S. Gordon [Iowa State University]

J. Chem. Theor. and Comp., **10**, 908–912, 2014.

Increasingly, modern computer systems comprise a multicore general-purpose processor augmented with a number of special purpose devices or accelerators connected via an external interface such as a PCI bus. The NVIDIA Kepler Graphical Processing Unit (GPU) and the Intel Phi are two examples of such accelerators. Accelerators offer peak performances that can be well above those of the host processor. How to exploit this heterogeneous environment for legacy application codes is not, however, straightforward. This paper considers how matrix operations in typical quantum chemical calculations can be migrated to the GPU and Phi systems.

GPU Accelerated Implementation of Density Functional Theory for Hybrid QM/MM Simulations

Matías A. Nitsche, Manuel Ferreria, Esteban E. Mocskos, Mariano C. González Lebrero [IQUIFIB, CONICET]

J. Chem. Theor. and Comp., **10**, 959–967, 2014.

The hybrid simulation tools (QM/MM) evolved into a fundamental methodology for studying chemical reactivity in complex environments. This paper presents an implementation of electronic structure calculations based on density functional theory. This development is optimized for performing hybrid molecular dynamics simulations by making use of graphic processors (GPU) for the most computationally demanding parts (exchange-correlation terms). The proposed implementation is able to take advantage of modern GPUs achieving acceleration in relevant portions between 20 to 30 times faster than the CPU version.

Nuclear Magnetic Shielding Constants from Quantum Mechanical/Molecular Mechanical Calculations Using Polarizable Embedding: Role of the Embedding Potential

Casper Steinmann [University of Southern Denmark], Jógvan Magnus Haugaard Olsen, Jacob Kongsted

J. Chem. Theor. and Comp., **10**, 981–988, 2014.

We present NMR shielding constants obtained through quantum mechanical/molecular mechanical (QM/MM) embedding calculations. Contrary to previous reports, we show that a relatively small QM region is sufficient, provided that a high-quality embedding potential is used. The calculated averaged NMR shielding constants of both acrolein and acetone solvated in water are based on a number of snapshots extracted from classical molecular dynamics simulations. We focus on the carbonyl chromophore in both molecules, which shows large solvation effects, and we study the convergence of shielding constants with respect to total system size and size of the QM region.

Ion Binding to Quadruplex DNA Stems. Comparison of MM and QM Descriptions Reveals Sizable Polarization Effects Not Included in Contemporary Simulations

Konstantinos Gkionis, Holger Kruse, James A. Platts, Arnošt Mládek, Jaroslav Koča, Jiří Šponer [Masaryk University]

J. Chem. Theor. and Comp., **10**, 1326–1340, 2014.

Molecular mechanical (MM) force fields are commonly employed for biomolecular simulations. Despite their success, the nonpolarizable nature of contemporary additive force fields limits their performance, especially in long simulations and when strong polarization effects are present. Guanine quadruplex D(R)NA molecules have been successfully studied by MM simulations in the past. Here, we provide a detailed comparison between quantum chemical (QM) DFT-D3 and MM potential energy surfaces of ion binding to G-stems and assess differences that may affect MM simulations.

QM and QM/MM (Cont'd)

Photophysics of Flavin Derivatives Absorbing in the Blue-Green Region: Thioflavins As Potential Cofactors of Photoswitches

Christel M. Marian [Heinrich Heine University Düsseldorf], Setsuko Nakagawa, Vidisha Rai-Constapel, Bora Karasulu, Walter Thiel

J. Phys. Chem. B., **118**, 1743–1753, 2014.

The purpose of this study was to find flavin derivatives with absorption maxima in the blue-green region of the visible spectrum that might be used as alternative cofactors in blue-light photoreceptors. To this end, the vertical absorption spectra of eight lumiflavin-related compounds were calculated by means of quantum chemical methods. The compounds differ from lumiflavin by the substitution of an S atom for an O atom at the 2- and/or 4-positions of the isoalloxazine core, the substitution of an N atom for a CH group in the 6- and/or 9-positions, or an extension of the π system at the 7- and 8-positions.

Role of Two Alternate Water Networks in Compound I Formation in P450eryF

Kakali Sen, Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Phys. Chem. B., **118**, 2810–2820, 2014.

The P450eryF enzyme (CYP107A1) hydroxylates 6-deoxyerythronolide B to erythronolide B during erythromycin synthesis by *Saccharopolyspora erythraea*. In many P450 enzymes, a conserved “acid-alcohol pair” is believed to participate in the proton shuttling pathway for O₂ activation that generates the reactive oxidant (Compound I, Cpd I). In CYP107A1, the alcohol-containing amino acid is replaced with alanine. The crystal structure of DEB bound to CYP107A1 indicates that one of the substrate hydroxyl groups (5-OH) may facilitate proton transfer during O₂ activation. We applied molecular dynamics (MD) and hybrid quantum mechanics/molecular mechanics (QM/MM) techniques to investigate substrate-mediated O₂ activation in CYP107A1.

Hybrid QM/MM Simulations of the Obelin Bioluminescence and Fluorescence Reveal an Unexpected Light Emitter

Shufeng Chen, Isabelle Navizet, Roland Lindh, Yajun Liu [Beijing Normal University], Nicolas Ferré

J. Phys. Chem. B., **118**, 2896–2903, 2014.

Obelia longissima, a tiny hydrozoan living in temperate and cold seas, features the Obelin photoprotein, which emits blue light. The Obelin bioluminescence and the Ca²⁺-discharged Obelin fluorescence spectra show multimodal characteristics that are currently interpreted by the concomitant participation of several light emitters. Up to now, the coelenteramide luminophore is thought to exist in different protonation states, one of them engaged in an ion-pair with the nearby residue, His22. Using hybrid quantum mechanics/molecular mechanics (QM/MM) calculations, we demonstrate that such an ion-pair cannot exist as a stable light emitter.

Comparative or Homology Modeling

Combining evolutionary information extracted from frequency profiles with sequence-based kernels for protein remote homology detection

Bin Liu [Harbin Institute of Technology Shenzhen Graduate School], Deyuan Zhang, Ruifeng Xu, Jinghao Xu, Xiaolong Wang, Qingcai Chen, Qiwen Dong, Kuo-Chen Chou

Bioinformatics. **30**, 472-479, 2014.

Owing to its importance in both basic research (such as molecular evolution and protein attribute prediction) and practical application, protein remote homology detection has attracted a great deal of interest. Here, we propose a novel approach, the so-called profile-based protein representation, to extract the evolutionary information via the frequency profiles. The latter can be calculated from the multiple sequence alignments generated by PSI-BLAST. Three top performing sequence-based kernels (SVM-Ngram, SVM-pairwise and SVM-LA) were combined with the profile-based protein representation. Various tests were conducted on a SCOP benchmark dataset that contains 54 families and 23 superfamilies.

Construction of an intermediate-resolution lattice model and re-examination of the helix-coil transition: a dynamic Monte Carlo simulation

Yantao Chen [Shenzhen University], Jiandong Ding

J. Biomol. Stru. and Dyn., **32**, 792-803, 2014.

In protein modeling, spatial resolution and computational efficiency are always incompatible. As a compromise, an intermediate-resolution lattice model has been constructed in the present work. Each residue is decomposed into four basic units, i.e. the α -carbon group, the carboxyl group, the imino group, and the side-chain group, and each basic coarse-grained unit is represented by a minimum cubic box with eight lattice sites. The spacing of the lattice is about 0.56 Å, holding the highest spatial resolution for the present lattice protein models. As the first report of this new model, the helix-coil transition of a polyalanine chain was examined via dynamic Monte Carlo simulation.

In silico and in vivo studies of molecular structures and mechanisms of AtPCS1 protein involved in binding arsenite and/or cadmium in plant cells

Noor Nahar, Aminur Rahman, Maria Moś, Tomasz Warzecha, Sibdas Ghosh, Khaled Hossain, Neelu N. Nawani, Abul Mandal [University of Skövde]

J. Mol. Mod., **20**, 2104, 2014.

This paper reports a continuation of our previous research on the *phytochelatin synthase1* (PCS1) gene involved in binding and sequestration of heavy metals or metalloids in plant cells [1]. Construction of a 3D structure of the *Arabidopsis thaliana* PCS1 protein and prediction of gene function by employing iterative implementation of the threading assembly refinement (I-TASSER) revealed that PC ligands (3GC-gamma-glutamylcysteine) and Gln50, Pro53, Ala54, Tyr55, Cys56, Ile102, Gly161, His162, Phe163, Asp204 and Arg211 residues are essential for formation of chelating complex with cadmium (Cd^{2+}) or arsenite (AsIII).

Assessing hERG Pore Models As Templates for Drug Docking Using Published Experimental Constraints: The Inactivated State in the Context of Drug Block

Christopher E. Dempsey [University of Bristol], Dominic Wright, Charlotte K. Colenso, Richard B. Sessions, Jules C. Hancox

J. Chem. Infor. and Mod. **54**, 601–612, 2014.

Many structurally and therapeutically diverse drugs interact with the human heart K^+ channel hERG by binding within the K^+ permeation pathway of the open channel, leading to drug-induced 'long QT syndrome'. Drug binding to hERG is often stabilized by inactivation gating. In the absence of a crystal structure, hERG pore homology models have been used to characterize drug interactions. Here we assess potentially inactivated states of the bacterial K^+ channel, KcsA, as templates for inactivated state hERG pore models in the context of drug binding using computational docking.

Ligand Docking

Molecular level activation insights from a NR2A/NR2B agonist

Weng JeongTou, Su-Sen Chang, Dongchuan Wu, Ted Weita Lai, Yu Tian Wang, Chung Y. Hsu, Calvin Yu-ChianChen [China Medical University Hospital]

J. Biomol. Stru. and Dyn., **32**, 683-693, 2014.

N-methyl D-aspartate receptors (NMDARs), a subclass of glutamate receptors have broad actions in neural transmission for major brain functions. Overactivation of NMDARs leading to “excitotoxicity” is the underlying mechanism of neuronal death in a number of neurological diseases, especially stroke. Much research effort has been directed toward developing pharmacological agents to modulate NMDAR actions for treating neurological diseases, in particular stroke. Here, we report that Alliin, a sulfoxide in fresh garlic, exhibits affinity toward NR2A as well as NR2B receptors based on virtual screening.

Ligand Binding Mode Prediction by Docking: Mdm2/Mdmx Inhibitors as a Case Study

Nagakumar Bharatham, Kavitha Bharatham, Anang A. Shelat, Donald Bashford [Saint Jude Children’s Research Hospital]

J.Chem. Infor. and Mod. **54**, 648–659, 2014.

This work tests alternative pipelines using several commonly used conformation generation programs (LigPrep, ConfGen, MacroModel, and Corina/Rotate) and docking programs (GOLD, Glide, MOE-dock, and AutoDock Vina) for their ability to reproduce known poses for a series of Mdmx and/or Mdm2 inhibitors, including several nutlins. Most combinations of these programs using default settings fail to find correct poses for the nutlins but succeed for all other compounds. Docking success for the nutlin class requires either computationally intensive conformational exploration or an “anchoring” procedure that incorporates knowledge of the orientation of the central imidazoline ring.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 49, March, 2014.

- 25-37 **Discovery of potent inhibitor for matrix metalloproteinase-9 by pharmacophore based modeling and dynamics simulation studies** ,Sukesh Kalva, E.R. Azhagiya Singam, V. Rajapandian, Lilly M. Saleena, V. Subramanian [Council of Scientific and Industrial Research, Adyar]

See Applications / Medicinal Chemistry and Drug Design.

- 38-46 **Pharmacophore model of the quercetin binding site of the SIRT6 protein** ,S. Ravichandran, N. Singh, D. Donnelly, M. Migliore, P. Johnson, C. Fishwick, B.T. Luke, B. Martin, S. Maudsley, S.D. Fugmann, R. Moaddel[National Institute on Aging]

See Applications / Medicinal Chemistry and Drug Design.

- 47-54 **Tautomerism in pyridazin-3(2H)-one: A theoretical study using implicit/explicit solvation models** ,Saeed Reza Emamian [Islamic Azad University], Luis Ramón Domingo, Sayyed Faramarz Tayyari

The tautomeric conversion of pyridazin-3(2H)-one **1** into pyridazin-3-ol **2** has been theoretically studied using density functional theory (DFT) methods at the B3LYP/6-311++G** level.

- 55-67 **Stereoselective propagation in free radical polymerization of acrylamides: A DFT study** ,Gülru Kayık, Nurcan Ş. Tüzün [Ayazaga Campus]

In this study stereospecific free radical polymerization of *N,N*-alkylamides [*N,N*-dimethylacrylamide (DMAAm), *N*-methyl-*N*-phenylacrylamide (MphAAm) and *N,N*-diphenylacrylamide (DPAAm)] is investigated with density functional theory (DFT) calculations. Model propagation reactions at dimeric stage are used to elucidate the effect of substituent bulkiness, temperature and solvent polarity on stereospecific addition modes.

- 68-79 **Discovery of novel anti-leishmanial agents targeting LdLip3 lipase** ,Saravanan Parameswaran, Prakash Saudagar, Vikash Kumar Dubey, Sanjukta Patra [Indian Institute of Technology Guwahati]

See Applications / Medicinal Chemistry and Drug Design.

- 80-90 **Characterization of CO₂ and mixed methane/CO₂ hydrates intercalated in smectites by means of atomistic calculations** ,Rubén Martos-Villa [Universidad de Cádiz], M. Pilar Mata, C. Ignacio Sainz-Díaz

The recent increase in anthropogenic CO₂ gas released to the atmosphere and its contribution to global warming make necessary to investigate new ways of CO₂ storage. Injecting CO₂ into subsurface CH₄hydrate reservoirs would displace some of the CH₄ in the hydrate crystal lattice, converting simple CH₄hydrates into either simple CO₂ hydrates or mixed CH₄—CO₂ hydrates. Molecular simulations were performed to determine the structure and behavior of CO₂ and mixed hydrate complexes in the interlayer of Na-rich montmorillonite and beidellite smectite.

- 91-98 **Toward activated homology models of the human M₁ muscarinic acetylcholine receptor** ,Sek Peng Chin, Michael J.C. Buckle [University of Malaya] , David K. Chalmers, Elizabeth Yuriev, Stephen W. Doughty

See Applications / Homology Modeling.

- 99-109 **Effect of ligand binding on the dynamics of trypsin. Comparison of different approaches** ,Elena Ermakova [Kazan Institute of Biochemistry and Biophysics RAS], Rauf Kurbanov

See Applications / Ligand Binding.

- 110-117 **Design of an interface peptide as new inhibitor of human glucose-6-phosphate dehydrogenase** ,Cristian Obiol-Pardo, Gema Alcarraz-Vizán, Santiago Díaz-Moralli, Marta Cascante, Jaime Rubio-Martinez [University of Barcelona and Institut de Recerca en Química Teòrica i Computacional (XRQTC)]

See Applications / Enzyme Catalysis.

Journal of Computational Chemistry, 35 (6), March, 2014.

- 415-426 **A polarizable dipole-dipole interaction model for evaluation of the interaction energies for N—H···O=C and C—H···O=C hydrogen-bonded complexes** ,Shu-Shi Li, Cui-Ying Huang, Jiao-Jiao Hao , Chang-Sheng Wang [Liaoning Normal University]

In this article, a polarizable dipole-dipole interaction model is established to estimate the equilibrium hydrogen bond distances and the interaction energies for hydrogen-bonded complexes containing peptide amides and nucleic acid bases.

- 427-444 **A survey of the parallel performance and accuracy of Poisson solvers for electronic structure calculations** ,Pablo García-Risueño [Humboldt Universität zu Berlin], Joseba Alberdi-Rodriguez, Micael J. T. Oliveira, Xavier Andrade, Michael Pippig, Javier Muguerza, Agustin Arruabarrena, Angel Rubio

Highly parallelizable routines have been implemented in a first-principle simulation code (OCTOPUS) to be used in our tests, so that reliable conclusions about the capability of methods to tackle large systems in cluster computing can be obtained from our work.

- 445-450 **A multilayered representation, quantum mechanical and molecular mechanics study of the CH₃F + OH⁻ reaction in water** ,Jie Chen, Yulong Xu ,Dunyou Wang [Shandong Normal University]

The bimolecular nucleophilic substitution (S_N2) reaction of CH₃F + OH⁻ in aqueous solution was investigated using a combined quantum mechanical and molecular mechanics approach.

- 451-466 **Is the DPT tautomerization of the long A·G Watson-Crick DNA base mispair a source of the adenine and guanine mutagenic tautomers? A QM and QTAIM response to the biologically**

important question ,Ol'ha O. Brovarets, Roman O. Zhurakivsky,Dmytro M. Hovorun [National Academy of Sciences of Ukraine]

See Methodology / QM and QM/MM.

467–478 **Perturbative treatment of anharmonic vibrational effects on bond distances: An extended langevin dynamics method** ,Tonghao Shen, Neil Qiang Su, Anan Wu ,Xin Xu [Xiamen University]

In this work, we first review the perturbative treatment of an oscillator with cubic anharmonicity. It is shown that there is a quantum-classical correspondence in terms of mean displacement, mean-squared displacement, and the corresponding variance in the first-order perturbation theory, provided that the amplitude of the classical oscillator is fixed at the zeroth-order energy of quantum mechanics $E_{QM}^{(0)}$.

479–487 **Characterization of the potential energy surfaces of two small but challenging noncovalent dimers: (P₂)₂ and (PCCP)₂** ,Eric Van Dornshuld , Gregory S. Tschumper [University of Mississippi]

This work characterizes eight stationary points of the P₂ dimer and six stationary points of the PCCP dimer, including a newly identified minimum on both potential energy surfaces. Full geometry optimizations and corresponding harmonic vibrational frequencies were computed with the second-order Møller–Plesset (MP2) electronic structure method and six different basis sets: aug-cc-pVXZ, aug-cc-pV(X+d)Z, and aug-cc-pCVXZ where X = T, Q.

495–505 **ChemNetworks: A complex network analysis tool for chemical systems** ,Abdullah Ozkanlar [Washington State University] ,Aurora E. Clark

This work discusses the *ChemNetworks* software, whose purpose is to process Cartesian coordinates of chemical systems into a network/graph formalism and apply topological network analyses that include network neighborhood, the determination of geodesic paths, the degree census, direct structural searches, and the distribution of defect states of network.

Journal of Computational Chemistry, 35 (7), March, 2014.

507–517 **Coupled-cluster reaction barriers of HO₂+H₂O+O₃: An application of the coupled-cluster//Kohn–Sham density functional theory model chemistry** ,Luís P. Viegas , António J. C. Varandas [Universidade de Coimbra]

In this work, we report a theoretical investigation concerning the use of the popular coupled-cluster//Kohn–Sham density functional theory (CC//KS-DFT) model chemistry, here applied to study the entrance channel of the HO₂+H₂O+O₃ reaction, namely by comparing CC//KS-DFT calculations with KS-DFT, MRPT2//CASSCF, and CC//CASSCF results from our previous investigations.

518–525 **Decoding the components of dynamics in three-domain proteins** ,Mateusz Maciejewski, Paul N. Barlow ,Nico Tjandra [National Institutes of Health, Bethesda]

See Applications / Protein Dynamics.

- 526–539 **Importance of ligand conformational energies in carbohydrate docking: Sorting the wheat from the chaff** ,Anita K. Nivedha, Spandana Makeneni, Bethany Lachele Foley, Matthew B. Tessier , Robert J. Woods [National University of Ireland]

See Applications / Protein Confirmation Analysis.

- 540–552 **Iron–sulfur bond covalency from electronic structure calculations for classical iron–sulfur clusters (pages)** ,Travis V. Harris and Robert K. Szilagy [Montana State University]

In this study of iron tetrathiolates, and classical [2Fe—2S] and [4Fe—4S] clusters with only thiolate ligands, we find that orbital compositions can vary significantly depending on whether they are derived from frontier orbitals, spin densities, or electron sharing indexes from “Atoms in Molecules” (AIM) theory.

- 553–564 **Conductor-like screening model for relaxed excited states: Implementation in the semiempirical method MSINDO** ,Katharina Krause, Thomas Bredow [Universität Bonn]

Two approaches to treat solvent polarization and reorientation effects for excited states of molecules and surfaces have been implemented in the recently developed MSINDO-sCIS method (Gadaczek, Krause, Hintze, Bredow, J. Chem. Theory Comput. 2011, 7, 3675).

- 565–585 **Electron localizability indicators from spinor wavefunctions** ,Alexey I. Baranov [Max Planck Institute for Chemical Physics of Solids]

For the fully relativistic 4-component many-electron wavefunction six flavors of electron localizability indicators (ELI) have been proposed. Their counterparts, suitable for the application to the 2-component wavefunctions, have been also derived.

- 586–594 **Effect of substitutionally boron-doped single-walled semiconducting zigzag carbon nanotubes on ammonia adsorption** ,Talapunur Vikramaditya and Kanakamma Sumithra [Hyderabad Campus]

We investigate the binding of ammonia on intrinsic and substitutionally doped semiconducting single-walled carbon nanotubes (SWCNTs) on the side walls using density functional calculations.

Journal of Computational Chemistry, 35 (8), March, 2014.

- 595–610 **A comprehensive conformational analysis of tryptophan, its ionic and dimeric forms** ,Uppala Purushotham , G. Narahari Sastry [CSIR-Indian Institute of Chemical Technology]

See Applications / Protein Confirmation Analysis.

- 611–621 **Code interoperability and standard data formats in quantum chemistry and quantum dynamics: The Q5/D5Cost data model** ,Elda Rossi, Stefano Evangelisti, Antonio Laganà, Antonio Monari, Sergio Rampino, Marco Verdicchio, Kim K. Baldridge, Gian Luigi Bendazzoli, Stefano Borini, Renzo Cimiraglia, Celestino Angeli, Peter Kallay, Hans P. Lüthi[ETH Zürich], Kenneth Ruud, José Sanchez-Marin, Anthony Scemama, Peter G. Szalay and Attila Tajti

See Methodology / QM and QM/MM.

- 622–633 **A general, recursive, and open-ended response code** ,Magnus Ringholm, Dan Jonsson , Kenneth Ruud [University of Tromsø—The Arctic University of Norway]

We present a new implementation of a recent open-ended response theory formulation for time- and perturbation-dependent basis sets (Thorvaldsen et al., J. Chem. Phys. 2008, 129, 214108) at the Hartree–Fock and density functional levels of theory.

- 634–643 **New accurate benchmark energies for large water clusters: DFT is better than expected** ,Tony Anacker [Chemnitz University of Technology] , Joachim Friedrich

In this work, we use MP2 and coupled-cluster with single, double, and perturbative triple excitations [CCSD(T)] as well as their corresponding explicitly correlated (F12) counterparts to compute the interaction energies of water icosamers.

- 644–656 **SSThread: Template-free protein structure prediction by threading pairs of contacting secondary structures followed by assembly of overlapping pairs** ,Kevin J. Maurice [15 Mitchell Ave]

See Applications / Protein Structure Prediction.

- 657–671 **Explicit proton transfer in classical molecular dynamics simulations** ,Maarten G. Wolf ,Gerrit Groenhof [University of Jyväskylä]

See Methodology / Molecular Dynamics.

- 672–681 **Voronota: A fast and reliable tool for computing the vertices of the Voronoi diagram of atomic balls** ,Kliment Olechnovič , Česlovas Venclovas [Vilnius University]

The Voronoi diagram of balls, corresponding to atoms of van der Waals radii, is particularly well-suited for the analysis of three-dimensional structures of biological macromolecules. Here, we present a simple and robust algorithm for computing the vertices of the Voronoi diagram of balls.

Journal of Molecular Modeling, 20 (3), March, 2014.

- 2177 **First-principles study of Carbz-PAHTDDT dye sensitizer and two Carbz-derived dyes for dye sensitized solar cells** ,Narges Mohammadi, Feng Wang [Swinburne University of Technology]

Two new carbazole-based organic dye sensitizers are designed and investigated *in silico*. These dyes are designed through chemical modifications of the π -conjugated bridge of a reference organic sensitizer known as Carbz-PAHTDDT (S9) dye.

- 2174 **Sequence and 3D structure based analysis of TNT degrading proteins in *Arabidopsis thaliana*** ,Amrita Bhattacharjee, Rahul Shubhra Mandal, Santasabuj Das, Sudip Kundu [University of Calcutta]

See Applications / Homology Modeling.

- 2171 **Ab-initio study of structural, electronic, and transport properties of zigzag GaP nanotubes** ,Anurag Srivastava [ABV-Indian Institute of Information Technology & Management Gwalior (M.P.)], Sumit Kumar Jain, Purnima Swarup Khare

Stability and electronic properties of zigzag ($3 \leq n \leq 16$) gallium phosphide nanotubes (GaP NTs) have been analyzed by employing a systematic ab-initio approach based on density functional theory using generalized gradient approximation with revised Perdew Burke Ernzerhoff type parameterization.

- 2169 **Rational design of organoboron derivatives as chemosensors for fluoride and cyanide anions and charge transport and luminescent materials for organic light-emitting diodes** ,Ruifa Jin [Chifeng University], Shanshan Tang, Dongmei Luo

The interactions between chemosensors, donor- π -acceptor (D- π -A) dipolar organoboron derivatives, and different (CN^- , F^- , Cl^- , and Br^-) anions have been theoretically investigated using DFT approaches.

- 2168 **Stimulation of N-glycoside transfer in deoxythymidine glycol: mechanism of the initial step in base excision repair** ,Ze-qin Chen [China West Normal University], Xiao-qiang Liu, Ying Xue

Thymine glycol (Tg), a toxic oxidative DNA lesion, is preferentially removed by endonuclease III (Endo III). To investigate the glycosylase activity of Endo III, the N-glycoside transfer mechanism in deoxythymidine glycol (dTg) is examined in this theoretical study based on the BHandHLYP/6-311++G(d,p) level of theory.

- 2165 **Atomistic simulation studies of the α/β -glucoside and galactoside in anhydrous bilayers: effect of the anomeric and epimeric configurations** ,Sara Ahmadi, Vijayan Manickam Achari, HockSeng Nguan, Rauzah Hashim [University of Malaya]

See Applications / Membrane Proteins and Lipid-Peptide Interaction.

- 2162 **In pursuit of negative Fukui functions: molecules with very small band gaps** ,Eleonora Echegaray, Sandra Rabi, Carlos Cárdenas, Farnaz Heidar Zadeh, Nataly Rabi, Sungmin Lee, James S. M. Anderson, Alejandro Toro-Labbe, Paul W. Ayers [McMaster University]

A justification for the likely presence of negative Fukui functions in molecules with small band gaps is given, and a computational study performed to check whether molecules with small band gaps have negative Fukui functions to a chemically significant extent is reported.

- 2159 **Self-consistent field convergence for proteins: a comparison of full and localized-molecular-orbital schemes** ,Christian R. Wick, Matthias Hennemann, James J. P. Stewart, Timothy Clark [University of Portsmouth]

Proteins in the gas phase present an extreme (and unrealistic) challenge for self-consistent-field iteration schemes because their ionized groups are very strong electron donors or acceptors, depending on their formal charge. We report full SCF calculations using the massively parallel EMPIRE code and linear scaling localized-molecular-orbital (LMO) calculations using Mopac2009.

- 2157 **Scytonin, a novel cyanobacterial photoprotective pigment: calculations of Raman spectroscopic biosignatures** ,Tereza Varnali [Bogazici University], Howell G. M. Edwards

The Raman spectrum of scytonin, a novel derivative of the parent scytonemin, is predicted from DFT calculations of the most stable, lowest energy, conformational structure.

- 2156 **Homology modeling, molecular dynamics and atomic level interaction study of snake venom 5' nucleotidase**, A. Syed Yasir Arafat, A. Arun, M. Ilamathi, J. Asha, P. R. Sivashankari, Cletus J. M. D'Souza, V. Sivaramakrishnan [SASTRA University], B. L. Dhananjaya

See Applications / Homology Modeling.

- 2154 **A B3LYP and MP2(full) theoretical investigation on the cooperativity effect between hydrogen-bonding and cation-molecule interactions and thermodynamic property in the 1: 2 (Na⁺: N-(Hydroxymethyl)acetamide) ternary complex**, Guo-rui Feng, Ting-ye Qi, Wen-jing Shi [The Third Hospital of Shanxi Medical University], Yu-xia Guo, Yu-jiang Zhang, Jun Guo, Li-xun Kang

The cooperativity effects between the O/N-H...O hydrogen-bonding and Na⁺...O cation-molecule interactions in the 1: 2 (Na⁺: N-(Hydroxymethyl)acetamide) systems were investigated at the B3LYP/6-311++G**, MP2(full)/6-311++G** and MP2(full)/aug-cc-pvtz levels.

- 2153 **A density functional theory study of paramagnetic cyclopentadienylcobalt(III) derivatives: fluoride versus cyanide**, Xiaozhen Gao, Xiuhui Zhang [Beijing Institute of Technology], Qian-shu Li, R. Bruce King, Henry F. Schaefer III

The cobalt(III) complexes Cp₂Co₂F₄ and Cp₂Co₂(CN)₄ have been studied by density functional theory methods as representatives of the experimentally known Cp₂Co₂X₄ species with the weak-field fluoride ligand and the strong-field cyanide ligand.

- 2152 **Theoretical study of the solvent effect on the aromaticity of benzene: a NICS analysis**, Georgia M. A. Junqueira [Universidade Federal de Juiz de Fora], Hélio F. Dos Santos

Nucleus-independent chemical shift (NICS) quantities for benzene–benzene and benzene–water species were obtained and are discussed in gas phase and in solution.

- 2151 **Stereodynamic study of the reaction H(²S) + ClO(²Π) → HO(²Π) + Cl(²P) via quasi-classical trajectory calculations**, Yanru Huang [Liaoning Shihua University]

Quasi-classical trajectory calculations were performed to investigate the stereodynamics of the reaction H(²S) + ClO(²Π) → HO(²Π) + Cl(²P) using the ground-state potential energy surface 1¹A'.

- 2150 **Density functional theory and molecular dynamics study of the uranyl ion (UO₂)²⁺**, Nicolás Rodríguez-Jeangros, Jorge M. Seminario [Texas A&M University]

The detection of uranium is very important, especially in water and, more importantly, in the form of uranyl ion (UO₂)²⁺, which is one of its most abundant moieties. Here, we report analyses and simulations of uranyl in water using ab initio modified force fields for water with improved parameters and charges of uranyl.

- 2149 **Theoretical study of absorption of 2,2,6,6-tetramethylpiperidine-1-oxoammonium cation (TEMPO) on TiO₂(110) rutile surface**, Israel Nieto-López, Luis Hernández-García, José Bonilla-Cruz, Mario Sanchez [Parque de Investigación e Innovación Tecnológica (PIIT)]

We present a theoretical study of the adsorption of 2,2,6,6-tetramethylpiperidine-1-oxoammonium cation (TEMPO) onto the TiO₂(110) surface rutile, investigating its bonding nature, electron properties and structural stability.

- 2147 **A computational model of the glycine tautomerization reaction in aqueous solution** ,Santiago Tolosa [Universidad de Extremadura], Antonio Hidalgo, Jorge A. Sansón

See Methodology / Molecular Dynamics.

- 2146 **An all-atom force field developed for Zn₄O(RCO₂)₆ metal organic frameworks** ,Yingxin Sun [Shanghai Institute of Technology], Huai Sun

An all-atom force field is developed for metal organic frameworks Zn₄O(RCO₂)₆ by fitting to quantum mechanics data.

- 2145 **Small cobalt clusters encapsulated inside Si₃₀C₃₀ nanocages: electronic and magnetic properties** Masoud Bezi Javan [Golestan University]

We investigated the structural, electronic, and magnetic properties of small Co_n clusters ($n = 2-6$) when they were endohedrally doped into Si₃₀C₃₀ nanocages using ab initio calculations based on density functional theory.

- 2144 **Nanomechanics of β -rich proteins related to neuronal disorders studied by AFM, all-atom and coarse-grained MD method** Karolina Mikulska, Janusz Strzelecki, Wiesław Nowak [Nicolaus Copernicus University]

See Applications / Protein Folding.

- 2143 **A new AMBER-compatible force field parameter set for alkanes** ,Alexei M. Nikitin [Russian Academy of Sciences], Yury V. Milchevskiy, Alexander P. Lyubartsev

We present a new force field parameter set for simulating alkanes. Its functional form and parameters are chosen to make it directly compatible with the AMBER94/99/12 family of force fields implemented in the available software.

- 2142 **Virtual screening of potential inhibitors from TCM for the CPSF30 binding site on the NS1A protein of influenza A virus** ,Haixin Ai, Li Zhang, Alan K. Chang, Hongyun Wei, Yuchen Che, Hongsheng Liu [Liaoning University]

Inhibition of CPSF30 function by the effector domain of influenza A virus of non-structural protein 1 (NS1A) protein plays a critical role in the suppression of host key antiviral response. In this study, structure-based molecular docking was utilized to screen more than 30,000 compounds from a Traditional Chinese Medicine (TCM) database.

- 2141 **3D-dynamic representation of DNA sequences** Piotr Wąż [Medical University of Gdańsk], Dorota Bielińska-Wąż

See Applications / Nucleic Acids.

- 2140 **Water-mediated potassium acetate intercalation in kaolinite as revealed by molecular simulation** ,Zoltán Ható, Éva Makó, Tamás Kristóf [University of Pannonia]

See Methodology / Molecular Dynamics.

- 2139 **Effect of protonation and hydrogen bonding on 2, 4, 6-substituted pyrimidine and its salt complex-experimental and theoretical evidence** ,Chithra Neelakanda Pillai, James Chellapan [Scott Christian College (Autonomous)]

Quantum molecular simulations of chemical systems can provide detailed information that is often inaccessible to direct experimental measurement. The experimental and computational evidence for the strength of these intra and intermolecular hydrogen are determined using vibrational spectra and quantum chemical calculations.

- 2138 **Encapsulation of alkyl and aryl derivatives of quaternary ammonium cations within cucurbit[n]uril ($n = 6,7$) and their inverted diastereomers: density functional investigations** ,Ishita A. Raja, Vivekanand V. Gobre, Rahul V. Pinjari, Shridhar P. Gejji [University of Pune, Ganeshkhind]

Electronic structure, vibrational frequencies, and ^1H chemical shifts of inclusion complexes between CB[n] ($n = 6,7$) or their inverted *i*CB[n] diastereomer hosts and quaternary diammonium viz., 1,6-hexyldiammonium (HDA) or p-xylyldiammonium (XYL) cationic guests are obtained from the density functional calculations.

- 2137 **Reaction mechanism of methylamine decomposition on Ru(0001): a density functional theory study** Cun-Qin Lv, Jian-Hong Liu, Xiao-fei Song, Yong Guo [Shanxi Datong University], Gui-Chang Wang

The reaction mechanism of methylamine decomposition on Ru(0001) has been systematically investigated by density functional theory slab calculations. The decomposition network has also been described.

- 2135 **Ab initio study of the structures and electronic states of small neutral and ionic DABCO – Ar_n clusters** ,Kevin Mathivon, Roberto Linguerr, Majdi Hochlaf [Université Paris-Est, Laboratoire Modélisation et Simulation Multi Echelle,]

In the present theoretical work, we investigated the stationary points (minima and transition states) on the ground state potential energy surfaces of neutral and ionic 1,4-diazabicyclo[2.2.2]octane (DABCO) – $\text{Ar}_n^{0,+1}$ ($n = 1-4$) clusters. As established in our systematic work on DABCO – Ar cluster (Mathivon et al., J Chem Phys 139:164306, 2013), the (R)MP2/aug-cc-pVDZ level is accurate enough for validating the prediction of stable forms.

- 2134 **The unrestricted local properties: application in nanoelectronics and for predicting radicals reactivity** ,Pavlo O. Dral [University of Erlangen-Nuremberg]

The local electron affinity (EA_L) and the local ionization energy (IE_L) are successfully used for predicting properties of closed-shell species for drug design and for nanoelectronics. Here the respective unrestricted Hartree-Fock variants of EA_L and IE_L , i.e., the unrestricted local electron affinity (UHF-EA_L) and ionization energy (UHF-IE_L), have been shown to be useful for predicting properties of open-shell species.

- 2133 **The X...Au interactions in the CF₃X (X = Cl, Br) ...Au_n (n = 2, 3, and 4) complexes**, Qiang Zhao [Zibo Vocational Institute]

I have performed quantum chemical calculations for the CF₃X (X = Cl, Br) ...Au_n (n = 2, 3, and 4) complexes at M05-2X/aug-cc-pVDZ(PP) level. Two types of optimized structures were obtained.

- 2132 **Investigation of plausible mechanistic pathways in hydrogenation of η^5 -(C₅H₅)₂Ta(H)=CH₂: an analysis using DFT and AIM techniques**, Soumya Ganguly Neogi, Anita Das, Pinaki Chaudhury [University of Calcutta]

In this manuscript, we investigate two plausible pathways for addition of H₂ across the bond Ta=C in η^5 -(C₅H₅)₂Ta(H)=CH₂.

- 2131 **Quantum chemical DFT study of the interaction between molecular oxygen and FeN₄ complexes, and effect of the macrocyclic ligand**, Adilson Luís Pereira Silva, Luciano Farias de Almeida, Aldaléa Lopes Brandes Marques, Hawbertt Rocha Costa, Auro Atsushi Tanaka, Albérico Borges Ferreira da Silva, Jaldyr de Jesus Gomes Varela Júnior [Universidade Federal do Maranhão]

Density functional theory (DFT) was used to examine the interaction between molecular oxygen (O₂) and macrocyclic iron complexes of the type FeN₄ during the formation of FeN₄-O₂ adducts.

- 2130 **Encapsulation of sodium radio-iodide in fullerene C₆₀**, Alejandro Valderrama [Instituto Politécnico Nacional, José Guzman]

In this work we have studied the well-known "Buckminsterfullerene" C₆₀ containing different amounts, from one to four molecules, of sodium radio-iodide (Na¹³¹I), with density functional theory geometrical optimizations and molecular dynamics at 310 K and atmospheric pressure.

- 2129 **2D-QSPR/DFT studies of aryl-substituted PNP-Cr-based catalyst systems for highly selective ethylene oligomerization**, Siyang Tang [East China University of Science and Technology], Zhen Liu, Xingwen Zhan, Ruihua Cheng, Xuelian He, Boping Liu

In this work, a series of aryl-substituted PNP-Cr catalysts were studied by two-dimensional quantitative structure-property relationship (QSPR) method based on density functional theory (DFT) calculations.

- 2128 **A theoretical study on ascorbic acid dissociation in water clusters**, Eugeni Demianenko [National Academy of Sciences of Ukraine], Mykola Ilchenko, Anatoliy Grebenyuk, Victor Lobanov, Oksana Tsendra

Dissociation of ascorbic acid in water has been studied by using a cluster model. It was examined by density functional theory (DFT) with the B3LYP, M06, and wB97XD functionals and a 6-311++G(d,p) basis set.

- 2127 **ReaxFF molecular dynamics simulations of the initial pyrolysis mechanism of unsaturated triglyceride**, Zhiqiang Zhang [Taiyuan University of Technology], Kefeng Yan, Jilong Zhang

See Applications / Protein Dynamics.

- 2125 **Theoretical investigation on the healing mechanism of divacancy defect in CNT growth by C₂H₂ and C₂H₄**, Bo Xiao, Xue-fang Yu, Yi-hong Ding [Jilin University]

Experimental studies have shown that chemical vapor decomposition method by using C_2H_2/C_2H_4 as carbon source could dramatically decrease the defects in prepared CNT. In the present paper, density functional theory is used to study the healing process of CNT with divacancy defect by C_2H_2/C_2H_4 molecule.

- 2124 **Different proton transfer channels for the transformation of zwitterionic alanine– $(H_2O)_{n=2-4}$ to nonzwitterionic alanine– $(H_2O)_{n=2-4}$: a density functional theory study**, Animesh K. Ojha [Motilal Nehru National Institute of Technology], Snehasis Bhunia

We report here the various possibilities of proton transfer between the zwitterionic and the non-zwitterionic form of alanine (Ala) via $(H_2O)_{n=2-4}$ clusters by calculating the transition state structures of zwitterionic alanine (ZAla)– $(H_2O)_{n=2-4}$ and non-zwitterionic alanine (Ala)– $(H_2O)_{n=2-4}$ complexes at B3LYP/6-311++G(d,p) and CAM-B3LYP/6-311++G(d,p) level of theory.

- 2120 **Insights into the influence of 5-HT_{2c} aminoacidic variants with the inhibitory action of serotonin inverse agonists and antagonists** Roberta Galeazzi [Dipartimento di Scienze della Vita e dell'Ambiente-Università Politecnica delle Marche], Luca Massaccesi, Francesco Piva, Giovanni Principato, Emilioano Laudadio

See Applications / Medicinal Chemistry and Drug Design.

- 2117 **In silico analysis on structure and DNA binding mode of AtNAC1, a NAC transcription factor from *Arabidopsis thaliana*** Qiankun Zhu, Jiaxin Zou, Mengli Zhu, Zubi Liu, Peichun Feng, Gaotao Fan, Wanjun Wang, Hai Liao

See Applications / Homology Modeling.

- 2116 **Homology modeling and virtual screening for antagonists of protease from yellow head virus** Sasimanas Unajak, Orathai Sawatdichaikul, Napat Songtawee, Siriluk Rattanabunyong, Anchalee Tassnakajon, Nontawith Areechon, Ikuo Hirono, Hidehiro Kondo, Pongsak Khunrae, Triwit Rattanaojpong, Kiattawee Choowongkamon [Kasetsart University]

See Applications / Homology Modeling.

- 2115 **Homodimers of Cytosine and 1-MethylCytosine. A DFT study of geometry, relative stability and H-NMR shifts in gas-phase and selected solvents**, Guvanchmyrat Paytakov, Leonid Gorb, Andriy Stepanyugin, Svitlana Samiylenko, Dmytro Hovorun, Jerzy Leszczynski [Jackson State University]

Dimers of cytosine and its N¹-methylated counterpart were investigated in gas-phase and in various solvents including chloroform, dimethylsulfoxide, and water. The studies were performed at DFT/M06-2X/6-31+G(d,p) level of theory.

- 2113 **The influence of anharmonic and solvent effects on the theoretical vibrational spectra of the guanine–cytosine base pairs in Watson–Crick and Hoogsteen configurations**, Attila Bende, Cristina M. Muntean [National Institute for Research and Development of Isotopic and Molecular Technologies]

See Applications / Nucleic Acids.

- 2111 **Charge distribution analysis in Agm+nclusters: molecular modeling and DFT calculations** ,Theodor Milek, Tibor Döpfer, Christian Neiss, Andreas Görling, Dirk Zahn [Friedrich-Alexander Universität Erlangen-Nürnberg]

Neutral and charged silver clusters Ag_{63}^{m+} and Ag_{113}^{m+} ($m=0, \dots, 20$) are investigated by simulated annealing molecular dynamics simulations.

- 2109 **Targeted studies on the interaction of nicotine and morin molecules with amyloid β -protein** Subramaniam Boopathi, Ponmalai Kolandaivel [Bharathiar University]

See Applications / Protein Dynamics.

- 2108 **Accurate simulation of geometry, singlet-singlet and triplet-singlet excitation of cyclometalated iridium(III) complex** ,Jian Wang, Fu-Quan Bai, Bao-Hui Xia, Hong-Xing Zhang [Jilin University], Tian Cui

In the current contribution, we present a critical study of the theoretical protocol used for the determination of the electronic spectra properties of luminescent cyclometalated iridium(III) complex, $[\text{Ir(III)}(\text{ppy})_2\text{H}_2\text{dcbpy}]^+$ (where, ppy = 2-phenylpyridine, H_2dcbpy = 2,2'-bipyridine-4,4'-dicarboxylic acid), considered as a representative example of the various problems related to the prediction of electronic spectra of transition metal complex.

- 2107 **Insights from quantum chemistry into piperazine-based ionic liquids and their behavior with regard to CO_2** ,Virginia Sanz, Rafael Alcalde, Mert Atilhan, Santiago Aparicio [University of Burgos]

The short-range properties of alkylpiperazine ionic liquids paired with propionate and lactate anions were analyzed and their affinity for CO_2 molecules studied using density functional theory.

- 2104 **In silico and in vivo studies of molecular structures and mechanisms of AtPCS1 protein involved in binding arsenite and/or cadmium in plant cells** ,Noor Nahar, Aminur Rahman, Maria Moś, Tomasz Warzecha, Sibdas Ghosh, Khaled Hossain, Neelu N. Nawani, Abul Mandal [University of Skövde]

See Methodology / Homology Modeling.

- 2099 **Mechanistic insights into mode of actions of novel oligopeptidase B inhibitors for combating leishmaniasis** ,Sukriti Goyal, Sonam Grover, Jaspreet Kaur Dhanjal, Manisha Goyal, Chetna Tyagi, Sajeev Chacko, Abhinav Grover [Jawaharlal Nehru University]

Leishmaniasis is an endemic disease caused by infection with one of several different species of protozoan parasite *Leishmania*. Oligopeptidase B (OPB) is a serine peptidase which plays a vital role in survival of the *Leishmania* parasite in the host (human) macrophage and help in attaining complete virulence. Inhibition of this peptidase would check the parasite growth inside the host organism and would thus control its infection.

- 2096 **Experimental and theoretical study of the mechanism of hydrolysis of substituted phenyl hexanoates catalysed by globin in the presence of surfactant** ,Selami Ercan, Nevin Arslan, Safak Ozhan Kocakaya, Necmettin Pirinccioglu [University of Dicle], Andrew Williams

The bimolecular rate constants for the globin- and alkali-catalysed hydrolysis of substituted phenyl hexanoates in the absence and presence of cetyltrimethylammonium bromide (CTAB) obey Brønsted equations with $\beta_{\text{lg}} = -0.53$ (globin-catalysed), -0.68 (globin-catalysed in CTAB), -0.34 (in water) and -0.74 (in CTAB), respectively.

- 2095 **Electronic and ionization spectra of 1,1-diamino-2,2-dinitroethylene, FOX-7**, Itamar Borges Jr. [Instituto Militar de Engenharia]

Singlet, triplet and ionized states of the energetic molecule 1,1-diamino-2,2-dinitroethylene, known as FOX-7 or DADNE, were investigated using the symmetry-adapted-cluster configuration interaction (SAC-CI) ab initio wave function. The 20 computed singlet transitions, with 2 exceptions, were bright.

- 2092 **Steered molecular dynamics identifies critical residues of the Nodamura virus B2 suppressor of RNAi** William J. Allen [Virginia Tech, Blacksburg], Michael R. Wiley, Kevin M. Myles, Zach N. Adelman, David R. Bevan

See Applications / Protein-Nucleic acids.

- 2088 **Theoretical study of the ring expansion reaction mechanism of cyclopropenylidene with azetidine** Xiaojun Tan [University of Jinan], Weihua Wang, Qiao Sun, Ying Jing, Ping Li

The mechanism for the ring expansion reaction between cyclopropenylidene and azetidine was systematically investigated employing second-order Møller–Plesset perturbation theory (MP2) in order to better understand the reactivity of cyclopropenylidene with the four-membered ring compound azetidine.

- 2087 **Density functional theory study of small X-doped Mg_n ($X = \text{Fe}, \text{Co}, \text{Ni}, n = 1-9$) bimetallic clusters: equilibrium structures, stabilities, electronic and magnetic properties**, Fanjie Kong [Yancheng Institute of Technology], Yanfei Hu

The geometries, stabilities, and electronic and magnetic properties of Mg_nX ($X = \text{Fe}, \text{Co}, \text{Ni}, n = 1-9$) clusters were investigated systematically within the framework of the gradient-corrected density functional theory.

- 2083 **Quantum chemical investigations of the water exchange mechanism on $[\text{Al}^{\text{III}}(\text{H}_2\text{O})_5(\text{L})]^{2+}$ as a function of the donor strength of the anionic L**, Basam M. Alzoubi, Immo Weber, Hans Hanauer, Ralph Puchta, Rudi van Eldik [University of Erlangen-Nürnberg]

Water exchange reactions of the complexes $[\text{Al}(\text{H}_2\text{O})_5\text{L}]^{2+} \cdot \text{H}_2\text{O}$ for $\text{L} = \rightarrow\text{OCN}^-, \text{F}^-, \text{CF}_3^-, \rightarrow\text{NC}^-, \rightarrow\text{CN}^-, \text{Cl}^-, \text{Br}^-, \text{H}^-, \text{SH}^-, \text{OH}^-, \rightarrow\text{NCO}^-, \rightarrow\text{NCS}^-, \rightarrow\text{SCN}^-, \text{CF}_3\text{CH}_2^-, \text{CH}_3^-, \text{Et}^-, \text{i-Pr}^-$ and $t\text{-but}^-$, were studied by DFT calculations (B3LYP/6-311+G**).

- 2082 **UV-vis absorption spectrum of a novel Ru(II) complex intercalated in DNA: $[\text{Ru}(2,2'\text{-bipy})(\text{dppz})(2,2'\text{-ArPy})]^+$** , Agisilaos Chantzis [Université de Lorraine Nancy], Thibaut Very, Stéphane Despax, Jean-Thomas Issenhuth, Alex Boeglin, Pascal Hébraud, Michel Pfeffer, Antonio Monari, Xavier Assfeld

See Applications / Protein-Nucleic acids.

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- 2078 **Experimental and theoretical assignment of the vibrational spectra of triazoles and benzotriazoles. Identification of IR marker bands and electric response properties** ,Saadullah G. Aziz, Shabaan A. Elroby, Abdulrahman Alyoubi, Osman I. Osman, Rifaat Hilal [King Abdulaziz University]

The FTIR spectra of a series of 1H- and 2H- 1,2,3- and 1,2,4- triazoles and benzotriazoles were measured in the solid state. Assignments of the observed bands were facilitated by computation of the spectra using the density functional B3LYP method with the 6-311++G** basis set. The theoretical spectra show very good agreement with experiment.

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About 105 Papers from more than 30 Journals are cited.

1 APPLICATIONS (67) Page 2

1.1 Small Molecules (15)

General and Model Systems	Page 2	QSAR	Page 5
Water and Solvation	Page 2	Host - Guest Systems	Page 6
Med. Chem. And Drug Design	Page 3		

1.2 Biopolymers (52)

Bioinformatics and Cheminformatics	Page 6	Protein-Protein Interactions	Page 15
Protein Secondary Structure	Page 7	Membrane Proteins	Page 15
Protein Conformational Analysis	Page 8	Protein Folding	Page 18
Protein Dynamics	Page 9	Protein-Nucleic Acids	Page 19
Ligand Binding	Page 11	Nucleic Acids	Page 19
Enzyme Catalysis	Page 13		

1.3 Polymers

1.4 Surfaces, Catalysts and Material Page 20

2 METHODOLOGY (19) Page 21

QSAR	Page 21	QM & QM/MM	Page 24
Potentials and Parameters	Page 22	Ligand Docking Modeling	Page 25
Molecular Dynamics	Page 23		

3 JOURNAL REVIEWS (5) Page 27

Journal of Molecular Graphics and Modeling, 50, April, 2014.
 Journal of Computational Chemistry, 35 (9), April, 2014.
 Journal of Computational Chemistry, 35 (10, 11), April, 2014.
 Journal of Molecular Modeling, 20 (4), April, 2014.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 40

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1. APPLICATIONS

1.1. Small Molecules

General and Model System

Princeton_TIGRESS: Protein geometry refinement using simulations and support vector machines

George A. Khoury, Phanourios Tamamis, Neesha Pinnaduwaage, James Smadbeck, Chris A. Kieslich and Christodoulos A. Floudas [Princeton University]

Proteins: Stru. Fun. & Bioinf., **82**, 794–814, 2014.

Protein structure refinement aims to perform a set of operations given a predicted structure to improve model quality and accuracy with respect to the native in a blind fashion. We initially developed a method tested using blind predictions during CASP10 which was officially ranked in 5th place among all methods in the refinement category. Here, we present Princeton_TIGRESS, which when benchmarked on all CASP 7,8,9, and 10 refinement targets, simultaneously increased GDT_TS 76% of the time with an average improvement of 0.83 GDT_TS points per structure.

Water and Solvation

Interaction of Charged Amino-Acid Side Chains with Ions: An Optimization Strategy for Classical Force Fields

Jens Kahlen, Leila Salimi, Marialore Sulpizi, Christine Peter, Davide Donadio [Max Planck Institute for Polymer Research]

J. Phys. Chem. B., **118**, 3960–3972, 2014.

Many well-established classical biomolecular force fields, fitted on the solvation properties of single ions, do not necessarily describe all the details of ion pairing accurately, especially for complex polyatomic ions. In this work, we analyzed how classical force fields can be optimized to yield a realistic description of these different aspects of ion pairing. Given the prominent role of the interactions of negatively charged amino-acid side chains and divalent cations in many biomolecular systems, we chose calcium acetate as a benchmark system to devise a general optimization strategy that we applied to two popular force fields, namely, GROMOS and OPLS-AA.



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Medicinal Chemistry and Drug Design

In silico investigation of medicinal spectrum of imidazoazines from the perspective of multitarget screening against malaria, tuberculosis and Chagas disease

Manoj Kumar, Barnita Makhal, Vinod Kumar Gupta, Anuj Sharma [Indian Institute of Technology Roorkee]

J. Mol.Graph. and Mod., **50**, 1-9, 2014.

A chemical database of 30 representative imidazoazines was built and screened against important tropical disease targets by computational docking. After three rounds of screening, an interaction profile was generated and analyzed. On the basis of binding energy and ligand efficiency, it was concluded that in general, imidazo-azine scaffold has a potential of being selective and simultaneous inhibitor against the five receptors Pf-dihydrofolate reductase, Pf-enoyl acyl carrier protein reductase, Pf-protein kinase 7, Mt-pantothenate synthetase and Mt-thymidine monophosphate kinase.

Computer-aided identification of novel 3,5-substituted rhodanine derivatives with activity against Staphylococcus aureus DNA gyrase

Malela M. Werner, Zhiyu Li, Randy J. Zauhar [University of the Sciences, Philadelphia]

Bioorg. and Med.Chem., **22**, 2176-2187, 2014.

Methicillin resistant Staphylococcus aureus (MRSA) is among the major drug resistant bacteria that persist in both the community and clinical settings due to resistance to commonly used antimicrobials. This continues to fuel the need for novel compounds that are active against this organism. For this purpose we have targeted the type IIA bacterial topoisomerase, DNA gyrase, an essential enzyme involved in bacterial replication, through the ATP-dependent supercoiling of DNA. The virtual screening tool Shape Signatures was applied to screen a large database for agents with shape similar to Novobiocin, a known gyrase B inhibitor.

GES Polypharmacology Fingerprints: A Novel Approach for Drug Repositioning

Violeta I. Pérez-Nueno [INRIA Nancy – Grand Est], Arnaud S. Karaboga, Michel Souchet, David W. Ritchie

J.Chem. Infor. and Mod. **54**, 720–734, 2014.

Polypharmacology is now recognized as an increasingly important aspect of drug design. We previously introduced the Gaussian ensemble screening (GES) approach to predict relationships between drug classes rapidly without requiring thousands of bootstrap comparisons as in current promiscuity prediction approaches. Here we present the GES “computational polypharmacology fingerprint” (CPF), the first target fingerprint to encode drug promiscuity information. The similarity between the 3D shapes and chemical properties of ligands is calculated using PARAFIT and our HPCC programs to give a consensus shape-plus-chemistry ligand similarity score.

ANN Multiscale Model of Anti-HIV Drugs Activity vs AIDS Prevalence in the US at County Level Based on Information Indices of Molecular Graphs and Social Networks

Humberto González-Díaz [University of the Basque Country UPV/EHU], Diana María Herrera-Ibatá, Aliuska Duardo-Sánchez, Cristian R. Munteanu, Ricardo Alfredo Orbegozo-Medina, Alejandro Pazos

J.Chem. Infor. and Mod. **54**, 744–755, 2014.

This work is aimed at describing the workflow for a methodology that combines chemoinformatics and pharmacoepidemiology methods and at reporting the first predictive model developed with this methodology. The new model is able to predict complex networks of AIDS prevalence in the US counties, taking into consideration the social determinants and activity/structure of anti-HIV drugs in preclinical assays. We trained different Artificial Neural Networks (ANNs) using as input information indices of social networks and molecular graphs. We used a Shannon information index based on the Gini coefficient to quantify the effect of income inequality in the social network.

Medicinal Chemistry and Drug Design (Cont'd)

The Valence State Combination Model: A Generic Framework for Handling Tautomers and Protonation States

Sascha Urbaczek, Adrian Kolodzik, Matthias Rarey
[University of Hamburg]

J.Chem. Infor. and Mod. **54**, 756–766, 2014.

The consistent handling of molecules is probably the most basic and important requirement in the field of cheminformatics. Reliable results can only be obtained if the underlying calculations are independent of the specific way molecules are represented in the input data. However, ensuring consistency is a complex task with many pitfalls, an important one being the fact that the same molecule can be represented by different valence bond structures. In order to achieve reliability, a cheminformatics system needs to solve two fundamental problems.

Uniting Cheminformatics and Chemical Theory To Predict the Intrinsic Aqueous Solubility of Crystalline Druglike Molecules

James L. McDonagh, Neetika Nath, Luna De Ferrari, Tanja van Mourik, John B. O. Mitchell [University of St. Andrews]

J.Chem. Infor. and Mod. **54**, 844–856, 2014.

We present four models of solution free-energy prediction for druglike molecules utilizing cheminformatics descriptors and theoretically calculated thermodynamic values. We make predictions of solution free energy using physics-based theory alone and using machine learning/quantitative structure–property relationship (QSPR) models. We also develop machine learning models where the theoretical energies and cheminformatics descriptors are used as combined input. These models are used to predict solvation free energy.

Structure Based Design, Synthesis, Pharmacophore Modeling, Virtual Screening, and Molecular Docking Studies for Identification of Novel Cyclophilin D Inhibitors

Koteswara Rao Valasani, Jhansi Rani Vangavaragu, Victor W. Day, Shirley ShiDu Yan [University of Kansas]

J.Chem. Infor. and Mod. **54**, 902–912, 2014.

Cyclophilin D (CypD) is a peptidyl prolyl isomerase F that resides in the mitochondrial matrix and associates with the inner mitochondrial membrane during the mitochondrial membrane permeability transition. CypD plays a central role in opening the mitochondrial membrane permeability transition pore (mPTP) leading to cell death and has been linked to Alzheimer's disease (AD). Because CypD interacts with amyloid beta (A β) to exacerbate mitochondrial and neuronal stress, it is a potential target for drugs to treat AD. Two-dimensional (2D) quantitative structure–activity relationship (QSAR) methods were applied to 40 compounds with known IC50 values.

Identification of Novel Serotonin Transporter Compounds by Virtual Screening

Mari Gabrielsen, Rafał Kurczab, Agata Siwek, Małgorzata Wolak, Aina W. Ravna, Kurt Kristiansen, Irina Kufareva, Ruben Abagyan, Gabriel Nowak, Zdzisław Chilmonczyk, Ingebrigt Sylte, Andrzej J. Bojarski [Institute of Pharmacology, Polish Academy of Sciences]

J.Chem. Infor. and Mod. **54**, 933–943, 2014.

The serotonin (5-hydroxytryptamine, 5-HT) transporter (SERT) plays an essential role in the termination of serotonergic neurotransmission by removing 5-HT from the synaptic cleft into the presynaptic neuron. It is also of pharmacological importance being targeted by antidepressants and psychostimulant drugs. Here, five commercial databases containing approximately 3.24 million drug-like compounds have been screened using a combination of two-dimensional (2D) fingerprint-based and three-dimensional (3D) pharmacophore-based screening and flexible docking into multiple conformations of the binding pocket detected in an outward-open SERT homology model.

Medicinal Chemistry and Drug Design (Cont'd)

Aqueous Poly(amidoamine) Dendrimer G3 and G4 Generations with Several Interior Cores at pHs 5 and 7: A Molecular Dynamics Simulation Study

Sajjad Kavyani, Sepideh Amjad-Iranagh, Hamid Modarress
[Amirkabir University of Technology]

J. Phys. Chem. B., **118**, 3257–3266, 2014.

Poly(amidoamine) (PAMAM) dendrimers play an important role in drug delivery systems, because the dendrimers are susceptible to gain unique features with modification of their structure such as changing their terminals or improving their interior core. To investigate the core improvement and the effect of core nature on PAMAM dendrimers, we studied two generations G3 and G4 PAMAM dendrimers with the interior cores of commonly used ethylenediamine (EDA), 1,5-diaminohexane (DAH), and bis(3-aminopropyl) ether (BAPE) solvated in water, as an aqueous dendrimer system, by using molecular dynamics simulation and applying a coarse-grained (CG) dendrimer force field.

Quantitative Structure-Activity Relations

Synthesis, biological evaluation and 3D-QSAR studies of new chalcone derivatives as inhibitors of human P-glycoprotein

Zahida Parveen, Gerda Brunhofer, Ishrat Jabeen, Thomas Erker, Peter Chiba, Gerhard F. Ecker[University of Vienna]

Bioorg. and Med.Chem., **22**, 2311–2319, 2014.

P-glycoprotein (P-gp) is an ATP-dependent multidrug resistance efflux transporter that plays an important role in anticancer drug resistance and in pharmacokinetics of medicines. Despite a large number of structurally and functionally diverse compounds, also flavonoids and chalcones have been reported as inhibitors of P-gp. The latter share some similarity with the well studied class of propafenones, but do not contain a basic nitrogen atom. Here, a set of 22 new chalcone derivatives were synthesized and evaluated in a daunomycin efflux inhibition assay using the CCRF.CEM.VCR1000 cell line.

QSAR Modeling of Imbalanced High-Throughput Screening Data in PubChem

Alexey V. Zakharov, Megan L. Peach, Markus Sitzmann, Marc C. Nicklaus [National Institutes of Health, DHHS, NCI-Frederick]

J.Chem. Infor. and Mod. **54**, 705–712, 2014.

We have used several such imbalanced PubChem HTS assays to test and develop strategies to efficiently build robust QSAR models from imbalanced data sets. Different descriptor types [Quantitative Neighborhoods of Atoms (QNA) and “biological” descriptors] were used to generate a variety of QSAR models in the program GUSAR. The models obtained were compared using external test and validation sets. We also report on our efforts to incorporate the most predictive of our models in the publicly available NCI/CADD Group Web services (<http://cactus.nci.nih.gov/chemical/apps/cap>).

Hsp90 Inhibitors, Part 2: Combining Ligand-Based and Structure-Based Approaches for Virtual Screening Application

Antonia Caroli, Flavio Ballante, Richard B. Wickersham, III, Federico Corelli, and Rino Ragno [Sapienza Università di Roma]

J.Chem. Infor. and Mod. **54**, 970–977, 2014.

Hsp90 continues to be an important target for pharmaceutical discovery. In this project, virtual screening (VS) for novel Hsp90 inhibitors was performed using a combination of Autodock and Surflex-Sim (LB) scoring functions with the predictive ability of 3-D QSAR models, previously generated with the 3-D QSAutogrid/R procedure. Extensive validation of both structure-based (SB) and ligand-based (LB), through realignments and cross-alignments, allowed the definition of LB and SB alignment rules.

Host-Guest Systems

Host-guest complexes of calix[4]tubes - prediction of ion selectivity by quantum chemical calculations VI

Svetlana Begel, Ralph Puchta [University of Erlangen-Nürnberg], Rudi van Eldik

J. Mol.Mod., **20**, 2200, 2014.

The selectivity of the bis(calix[4]arene)tetraethylene abbreviated as calix[4]tube for the endohedral complexation of alkali and alkaline earth metal ions, was predicted on the basis of structures and complex formation energies computed with three different quantum chemical methods: DFT LANL2DZp/LANL2DZp), PM3/SPASS, and PM6. A comparison with published X-ray structures demonstrated that the most reliable results were achieved applying DFT calculations.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Integrating open-source software applications to build molecular dynamics systems

Bruce M. Allen [University of Denver], Paul K. Predecki, Maciej Kumosa

J. Comp. Chem., **35**, 756–764, 2014.

Three open-source applications, NanoEngineer-1, packmol, and mis2lmp are integrated using an open-source file format to quickly create molecular dynamics (MD) cells for simulation. The three software applications collectively make up the open-source software (OSS) suite known as MD Studio (MDS). The software is validated through software engineering practices and is verified through simulation of the diglycidyl ether of bisphenol-a and isophorone diamine (DGEBA/IPD) system.

VCMM: A visual tool for continuum molecular modeling

Shiyang Bai, Benzhuo Lu [Chinese Academy of Sciences]

J. Mol.Graph. and Mod., **50**, 44-49, 2014.

This paper describes the design and function of a visualization tool, VCMM, for visualizing and analyzing data, and interfacing solvers for generic continuum molecular modeling. In particular, an emphasis of the program is to treat the data set based on unstructured mesh as used in finite/boundary element simulations, which largely enhances the capabilities of current visualization tools in this area that only support structured mesh. VCMM is segmented into molecular, meshing and numerical modules. The capabilities of molecular module include molecular visualization and force field assignment.

Bioinformatics and Cheminformatics (Cont'd)

HADDOCK2P2I: A Biophysical Model for Predicting the Binding Affinity of Protein–Protein Interaction Inhibitors

Panagiotis L. Kastitis, João P. G. L. M. Rodrigues, Alexandre M. J. J. Bonvin [Utrecht University]

J.Chem. Infor. and Mod. **54**, 826–836, 2014.

The HADDOCK score, a scoring function for both protein–protein and protein-nucleic acid modeling, has been successful in selecting near-native docking poses in a variety of cases, including those of the CAPRI blind prediction experiment. However, it has yet to be optimized for small molecules, and in particular inhibitors of protein–protein interactions, that constitute an “unmined gold reserve” for drug design ventures. We describe here HADDOCK2P2I, a biophysical model capable of predicting the binding affinity of protein–protein complex inhibitors close to experimental error (2-fold larger).

Automating human intuition for protein design

Lucas G. Nivón, Sinisa Bjelic, Chris King , David Baker [University of Washington]

Proteins: Stru. Fun. & Bioinf., **82**, 858–866, 2014.

In the design of new enzymes and binding proteins, human intuition is often used to modify computationally designed amino acid sequences prior to experimental characterization. The manual sequence changes involve both reversions of amino acid mutations back to the identity present in the parent scaffold and the introduction of residues making additional interactions with the binding partner or backing up first shell interactions. Here we introduce a benchmark for evaluating the ability of automated methods to recapitulate the sequence changes made to computer-generated models by human designers, and use it to assess alternative computational methods.

Protein Secondary Structure

Context-Based Features Enhance Protein Secondary Structure Prediction Accuracy

Ashraf Yaseen ,Yaohang Li [Old Dominion University]

J.Chem. Infor. and Mod. **54**, 992–1002, 2014.

We report a new approach of using statistical context-based scores as encoded features to train neural networks to achieve secondary structure prediction accuracy improvement. The context-based scores are pseudo-potentials derived by evaluating statistical, high-order inter-residue interactions, which estimate the favorability of a residue adopting certain secondary structure conformation within its amino acid environment. Encoding these context-based scores as important training and prediction features provides a way to address a long-standing difficulty in neural network-based secondary structure predictions of taking interdependency among secondary structures of neighboring residues into account.

Protein Conformational Analysis

Exploring the Conformational Dynamics of Alanine Dipeptide in Solution Subjected to an External Electric Field: A Nonequilibrium Molecular Dynamics Simulation

Han Wang [Freie Universität Berlin], Christof Schütte, Giovanni Ciccotti, and Luigi Delle Site

J. Chem. Theor. and Comp., **10**, 1376–1386, 2014.

In this paper, we investigate the conformational dynamics of alanine dipeptide under an external electric field by nonequilibrium molecular dynamics simulation. We consider the case of a constant and of an oscillatory field. In this context, we propose a procedure to implement the temperature control, which removes the irrelevant thermal effects of the field. For the constant field different time-scales are identified in the conformational, dipole moment, and orientational dynamics.

Improving the accuracy of protein stability predictions with multistate design using a variety of backbone ensembles

James A. Davey and Roberto A. Chica[University of Ottawa]

Proteins: Stru. Fun. & Bioinf., **82**, 771–784, 2014.

In this study, we aimed to improve the accuracy of protein stability predictions made with MSD by using a variety of backbone ensembles to recapitulate the experimentally measured stability of 85 *Streptococcal* protein G domain β 1 sequences. Ensembles tested here include an NMR ensemble as well as those generated by molecular dynamics (MD) simulations, by Backrub motions, and by PertMin, a new method that we developed involving the perturbation of atomic coordinates followed by energy minimization.

Molecular dynamics study of HIV-1 RT-DNA-nevirapine complexes explains NNRTI inhibition and resistance by connection mutations

R. S. K. Vijayan, Eddy Arnold, Kalyan Das [Rutgers University]

Proteins: Stru. Fun. & Bioinf., **82**, 815–829, 2014.

HIV-1 reverse transcriptase (RT) is a multifunctional enzyme that is targeted by nucleoside analogs (NRTIs) and non-nucleoside RT inhibitors (NNRTIs). NNRTIs are allosteric inhibitors of RT, and constitute an integral part of several highly active antiretroviral therapy regimens. Under selective pressure, HIV-1 acquires resistance against NNRTIs primarily by selecting mutations around the NNRTI pocket. We performed 50-ns molecular dynamics (MD) simulations, followed by essential dynamics, free-energy landscape analyses, and network analyses of RT-DNA, RT-DNA-nevirapine (NVP), and N348I/T369I mutant RT-DNA-NVP complexes.

Dynamic Behavior of the Active and Inactive States of the Adenosine A2A Receptor

Sangbae Lee, Supriyo Bhattacharya, Reinhard Grisshammer, Christopher Tate, Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J. Phys. Chem. B., **118**, 3355–3365, 2014.

The adenosine A2A receptor (A2AR) belongs to the superfamily of membrane proteins called the G-protein-coupled receptors (GPCRs) that form one of the largest superfamilies of drug targets. Deriving thermostable mutants has been one of the strategies used for crystallization of A2AR in both the agonist and antagonist bound conformational states. The crystal structures do not reveal differences in the activation mechanism of the mutant receptors compared to the wild type receptor, that have been observed experimentally. These differences stem from the dynamic behavior of the mutant receptors.

Protein Conformational Analysis (Cont'd)

Multiple Scale Dynamics in Proteins Probed at Multiple Time Scales through Fluctuations of NMR Chemical Shifts

Paolo Calligari [International School for Advanced Studies-SISSA/ISAS], Daniel Abergel

J. Phys. Chem. B., **118**, 3823–3831, 2014.

Fluctuations of NMR resonance frequency shifts and their relation with protein exchanging conformations are usually analyzed in terms of simple two-site jump processes. However, this description is unable to account for the presence of multiple time scale dynamics. In this work, we present an alternative model for the interpretation of the stochastic processes underlying these fluctuations of resonance frequencies. Time correlation functions of ¹⁵N amide chemical shifts computed from molecular dynamics simulations (MD) were analyzed in terms of a transiently fractional diffusion process.

Protein Dynamics

Molecular-Level Understanding of Protein Adsorption at the Interface between Water and a Strongly Interacting Uncharged Solid Surface

Matthew J. Penna, Milan Mijajlovic, Mark J. Biggs [The University of Adelaide]

J. Am. Chem. Soc., 2013, **136**, 5323–5331, 2014.

Although protein adsorption on solids is of immense relevance, experimental limitations mean there is still a remarkable lack of understanding of the adsorption mechanism, particularly at a molecular level. By subjecting 240+ molecular dynamics simulations of two peptide/water/solid surface systems to statistical analysis, a generalized molecular level mechanism for peptide adsorption has been identified for uncharged surfaces that interact strongly with the solution phase.

Quantum Mechanical Calculation of Noncovalent Interactions: A Large-Scale Evaluation of PMx, DFT, and SAPT Approaches

Amanda Li, Hari S. Muddana, Michael K. Gilson [University of California San Diego]

J. Chem. Theor. and Comp., **10**, 1563–1575, 2014.

QM calculations of noncovalent interactions are uniquely useful as tools to test and improve molecular mechanics force fields and to model the forces involved in biomolecular binding and folding. Because the more computationally tractable QM methods necessarily include approximations, which risk degrading accuracy, it is essential to evaluate such methods by comparison with high-level reference calculations. Here, we use the extensive Benchmark Energy and Geometry Database (BEGDB) of CCSD(T)/CBS reference results to evaluate the accuracy and speed of widely used QM methods for over 1200 chemically varied gas-phase dimers.

Dipeptide Aggregation in Aqueous Solution from Fixed Point-Charge Force Fields

Andreas W. Götz, Denis Bucher, Steffen Lindert, J. Andrew McCammon [University of California San Diego]

J. Chem. Theor. and Comp., **10**, 1631–1637, 2014.

The description of aggregation processes with molecular dynamics simulations is a playground for testing biomolecular force fields, including a new generation of force fields that explicitly describe electronic polarization. In this work, we study a system consisting of 50 glycyl-L-alanine (Gly-Ala) dipeptides in solution with 1001 water molecules. Neutron diffraction experiments have shown that at this concentration, Gly-Ala aggregates into large clusters. However, general-purpose force fields in combination with established water models can fail to correctly describe this aggregation process, highlighting important deficiencies in how solute–solute and solute–solvent interactions are parametrized in these force fields.

Protein Dynamics (Cont'd)

Theoretical tests of the mechanical protection strategy in protein nanomechanics

Mateusz Chwastyk, Albert Galera-Prat, Mateusz Sikora, Àngel Gómez-Sicilia, Mariano Carrión-Vázquez, Marek Cieplak [Polish Academy of Sciences]

We study examples of such systems within a coarse-grained structure-based model. We consider systems with various ratios of mechanostability for the host and guest molecules and compare them to experimental results involving cohesin I as the guest molecule. For a comparison, we also study the force-displacement patterns in proteins that are linked in a serial fashion. We find that the mechanostability of the guest is similar to that of the isolated or serially linked protein

Proteins: Stru. Fun. & Bioinf., **82**, 717–726, 2014.

The Stability of a β -Hairpin Is Altered by Surface–Water Interactions under Confinement

J. Srinivasa Rao, Micholas Dean Smith, Luis Cruz [Drexel University]

J. Phys. Chem. B., **118**, 3517–3523, 2014.

Understanding protein folding and stability in in vivo confined environments is a challenging problem from both experimental and computational points of views. Despite recent insights, an appreciation and complete understanding of how the solvent influences the structure and stability of proteins under complex confined environments is still lacking. Here, using all-atom molecular dynamics simulations in explicit solvent, we report the effects of confinement on the lifetime of a metastable β -hairpin structure in the A β (21–30) decapeptide.

Sensitivity of Water Dynamics to Biologically Significant Surfaces of Monomeric Insulin: Role of Topology and Electrostatic Interactions

Kushal Bagchi, Susmita Roy [St. Joseph's College for Arts and Science]

J. Phys. Chem. B., **118**, 3805–3813, 2014.

In addition to the biologically active monomer of the protein insulin circulating in human blood, the molecule also exists in dimeric and hexameric forms that are used as storage. The insulin monomer contains two distinct surfaces, namely, the dimer forming surface (DFS) and the hexamer forming surface (HFS), that are specifically designed to facilitate the formation of the dimer and the hexamer, respectively. In order to characterize the structural and dynamical behavior of interfacial water molecules near these two surfaces (DFS and HFS), we performed atomistic molecular dynamics simulations of insulin with explicit water.

New Insights into the Thermal Stability of the Smectic C Phase

François Porzio, Etienne Levert, Richard Vadnais, Armand Soldera [Université de Sherbrooke]

J. Phys. Chem. B., **118**, 4037–4043, 2014.

Subtle differences in the molecular structure of mesogens can lead to very different experimental polymorphisms. The smectic C (SmC) phase can actually be exhibited by one isomer and not the other, or the range of temperature can be completely different. Unveiling the deep connection between atomic structure and the very existence of the SmC phase will lead to the design of new performing liquid crystalline materials for ferroelectric or nonlinear optical applications. Our approach is based on running molecular dynamics simulation from an initial SmC arrangement of molecules.

Protein Dynamics (Cont'd)

Structural, Dynamic, and Transport Properties of Concentrated Aqueous Sodium Chloride Solutions under an External Static Electric Field

Gan Ren, Rui Shi, Yanting Wang [Chinese Academy of Sciences]

J. Phys. Chem. B., **118**, 4404–4411, 2014.

In the absence of an external electric field, it has already been known that ion clusters are formed instantaneously in moderately concentrated ionic solutions. In this work, we use molecular dynamics (MD) simulations to investigate the changes of structural, dynamic, and transport properties in a sodium chloride solution under an external electric field from the ion cluster perspective. Our MD simulation results indicate that, with a strong external electric field $E (\geq 0.1 \text{ V/nm})$ applied, ion clusters become smaller and less net charged, and the structures and dynamics as well as transport properties of the ion solution become anisotropic.

Ligand Binding/Docking

Binding free energies for nicotine analogs inhibiting cytochrome P450 2A6 by a combined use of molecular dynamics simulations and QM/MM-PBSA calculations

Haiting Lu, Xiaoqin Huang, Mohamed Diwan M. AbdulHameed, Chang-Guo Zhan [University of Kentucky]

Bioorg. and Med.Chem., **22**, 2149-2156, 2014.

Molecular dynamics (MD) simulations and hybrid quantum mechanical/molecular mechanical (QM/MM) calculations have been performed to explore the dynamic behaviors of cytochrome P450 2A6 (CYP2A6) binding with nicotine analogs (that are typical inhibitors) and to calculate their binding free energies in combination with Poisson–Boltzmann surface area (PBSA) calculations. The combined MD simulations and QM/MM-PBSA calculations reveal that the most important structural parameters affecting the CYP2A6-inhibitor binding affinity are two crucial internuclear distances, that is, the distance between the heme iron atom of CYP2A6 and the coordinating atom of the inhibitor, and the hydrogen-bonding distance between the N297 side chain of CYP2A6 and the pyridine nitrogen of the inhibitor.

Novel hydrazine derivatives as selective DPP-IV inhibitors: findings from virtual screening and validation through molecular dynamics simulations

Omprakash Tanwar, Girdhar Singh Deora, Lalima Tanwar, Gautam Kumar, Sridhara Janardhan, Md. Mumtaz Alam, Md. Shaquiquzzaman, Mymoona Akhter [Bioinformatics Infrastructure Facility (BIF)]

J. Mol.Mod., **20**, 2118, 2014.

The present study demonstrates and validates the discovery of two novel hydrazine derivatives as selective dipeptidyl peptidase-IV (DPP-IV) inhibitors. Virtual screening (VS) of publicly available databases was performed using virtual screening workflow (VSW) of Schrödinger software against DPP-IV and the most promising hits were selected. Selectivity was further assessed by docking the hits against homology modeled structures of DPP8 and DPP9. Two novel hydrazine derivatives were selected for further studies based on their selectivity threshold.

Ligand Binding / Docking (Cont'd)

Enhanced stability of a naringenin/2,6-dimethyl β -cyclodextrin inclusion complex: Molecular dynamics and free energy calculations based on MM- and QM-PBSA/GBSA

Waratchada Sangpheak, Wasinee Khuntawee, Peter Wolschann, Piamsook Pongsawasdi, Thanyada Rungrotmongkol [Chulalongkorn University]

J. Mol.Graph. and Mod., **50**, 10-15, 2014.

The structure, dynamic behavior and binding affinity of the inclusion complexes between naringenin and the two cyclodextrins (CDs), β -CD and its 2,6-dimethyl derivative (DM- β -CD), were theoretically studied by multiple molecular dynamics simulations and free energy calculations. Naringenin most likely prefers to bind with CDs through the phenyl ring. Although a lower hydrogen bond formation of naringenin with the 3-hydroxyl group of DM- β -CD (relative to β -CD) was observed, the higher cavity could encapsulate almost the whole naringenin molecule.

Designing of multi-targeted molecules using combination of molecular screening and in silico drug cardiotoxicity prediction approaches

Birce Buturak, Serdar Durdagi, Sergei Y. Noskov, A. Tugba Ozal Ildeniz [Kadir Has University]

J. Mol.Graph. and Mod., **50**, 16-34, 2014.

We have previously investigated and reported a set of phenol- and indole-based derivatives at the binding pockets of carbonic anhydrase isoenzymes using in silico and in vitro analyses. In this study, we extended our analysis to explore multi-targeted molecules from this set of compounds. Thus, 26 ligands are screened at the binding sites of 229 proteins from 5 main enzyme family classes using molecular docking algorithms. Derived docking scores are compared with reported results of ligands at carbonic anhydrase I and II isoenzymes. Results showed potency of multi-targeted drugs of a few compounds from investigated ligand set.

Definition of the binding mode of phosphoinositide 3-kinase α -selective inhibitor A-66S through molecular dynamics simulation

Xiaoli Bian, Wangqing Dong, Yang Zhao, Rui Sun, Wanjun Kong, Yiping Li [Xi'an Jiaotong University]

J. Mol.Mod., **20**, 2166, 2014.

Activation of the phosphatidylinositol 3-kinase α (PI3K α) is commonly observed in human cancer and is critical for tumor progression, which has made PI3K α an attractive target for anticancer drug discovery. To systematically investigate the binding mode of A-66S, a new selective PI3K α inhibitor for PI3K α , molecular docking, molecular dynamics simulation and ensuing energetic analysis were performed. The binding free energy between PI3K α and A-66S is $-11.27 \text{ kcal}\cdot\text{mol}^{-1}$ using MMPBSA method, while $-14.67 \text{ kcal}\cdot\text{mol}^{-1}$ using MMGBSA method, which is beneficial for the binding, and the van der Waals/hydrophobic and electrostatic interactions are critical for the binding.

Molecular interaction of PCB180 to human serum albumin: insights from spectroscopic and molecular modelling studies

Senbiao Fang, Huanhuan Li, Tao Liu, Hongxia Xuan, Xin Li, Chunyan Zhao [Lanzhou University]

J. Mol.Mod., **20**, 2098, 2014.

Polychlorinated biphenyls (PCBs) are potentially hazardous to the environment because of their chemical stability and biological toxicity. In this study, we identified the binding mode of a representative PCB180 to human serum albumin (HSA) using fluorescence and MD simulation methods. PCB180 bound exactly at subdomain IIIA of HSA based on the fluorescence study along with site marker displacement experiments. PCB180 also induced conformational changes that were governed mainly by hydrophobic forces. MD studies and free energy calculations also made important contributions to the understanding of the effects of an HSA-PCB180 system on conformational changes.

Ligand Binding / Docking (Cont'd)

Interference of Boswellic Acids with the Ligand Binding Domain of the Glucocorticoid Receptor

Thomas Scior [Benemérita Universidad Autónoma de Puebla], Moritz Verhoff, Itzel Gutierrez-Aztatzi, Hermann P.T. Ammon, Stefan Laufer, Oliver Werz

J.Chem. Infor. and Mod. **54**, 978–986, 2014.

Boswellic acids (BAs) possess anti-inflammatory properties in various biological models with similar features to those of glucocorticoids (GCs), such as suppression of the release of pro-inflammatory cytokines. Hence, the molecular mechanism of BAs responsible for their anti-inflammatory features might be attributable to interference with the human glucocorticoid receptor (GR). Due to obvious structural similarities with GCs, we conducted pharmacophore studies as well as molecular docking simulations of BAs as putative ligands at the ligand binding site (LBS) of the GR in distinct functional states.

Enzyme Catalysis

A QM/MM Study of the L-Threonine Formation Reaction of Threonine Synthase: Implications into the Mechanism of the Reaction Specificity

Mitsuo Shoji [University of Tsukuba], Kyohei Hanaoka, Yuzuru Ujiie, Wataru Tanaka, Daiki Kondo, Hiroaki Umeda, Yoshikazu Kamoshida, Megumi Kayanuma, Katsumasa Kamiya, Kenji Shiraishi, Yasuhiro Machida, Takeshi Murakawa, Hideyuki Hayashi

J. Am. Chem. Soc., 2013, **136**, 4525–4533, 2014.

Threonine synthase catalyzes the most complex reaction among the pyridoxal-5'-phosphate (PLP)-dependent enzymes. The important step is the addition of a water molecule to the C β –C α double bond of the PLP- α -aminocrotonate aldimine intermediate. Transaldimination of this intermediate with Lys61 as a side reaction to form α -ketobutyrate competes with the normal addition reaction. In order to elucidate the detailed mechanism of this “product-assisted catalysis”, we performed comparative QM/MM calculations with an exhaustive search for the lowest-energy-barrier reaction pathways starting from PLP- α -aminocrotonate aldimine intermediate.

Recognition of 2',5'-linked oligoadenylates by human ribonuclease L: molecular dynamics study

Kamil Maláč, Ivan Barvík [Charles University]

J. Mol.Mod., **20**, 2123, 2014.

The capability of current MD simulations to be used as a tool in rational design of agonists of medically interesting enzyme RNase L was tested. Dimerization and enzymatic activity of RNase L is stimulated by 2',5'-linked oligoadenylates (pA25A25A; 2-5A). First, it was necessary to ensure that a complex of monomeric human RNase L and 25A was stable in MD simulations. It turned out that Glu131 had to be protonated. The non-protonated Glu131 caused dissociation of 2-5A from RNase L. Because of the atypical 2'-5' internucleotide linkages and a specific spatial arrangement of the 25A trimer, when a single molecule carries all possible conformers of the glycosidic torsion angle, several versions of the AMBER force field were tested.

Enzyme Catalysis (Cont'd)

Comparison of *ab Initio*, DFT, and Semiempirical QM/MM Approaches for Description of Catalytic Mechanism of Hairpin Ribozyme

Vojtěch Mlýnský, Pavel Banáš, Jiří Šponer, Marc W. van der Kamp, Adrian J. Mulholland, Michal Otyepka [Palacky University]

J. Chem. Theor. and Comp. **10**, 1608–1622, 2014.

We have analyzed the capability of state-of-the-art multiscale computational approaches to provide atomic-resolution electronic structure insights into possible catalytic scenarios of the hairpin ribozyme by evaluating potential and free energy surfaces of the reactions by various hybrid QM/MM methods. The hairpin ribozyme is a unique catalytic RNA that achieves rate acceleration similar to other small self-cleaving ribozymes but without direct metal ion participation. Guanine 8 (G8) and adenine 38 (A38) have been identified as the catalytically essential nucleobases.

How Important Is the Synclinal Conformation of Sulfonylureas To Explain the Inhibition of AHAS: A Theoretical Study

Gonzalo A. Jaña [Universidad Andres Bello], Eduardo J. Delgado, and Fabiola E. Medina

J. Chem. Infor. and Mod. **54**, 926–932, 2014.

The inhibitory activity of 15 sulfonylureas on acetohydroxyacid synthase (AHAS) is addressed theoretically in order to stress how important the conformation is to explain their differences as AHAS inhibitors. The study includes calculations in gas phase, solution, and in the enzymatic environment. The results suggest that both the activation Gibbs free energy and Gibbs free energy change associated with the conformational change in solution allow for determining if sulfonylureas should have high or low inhibition activity.

Targeting Dynamic Pockets of HIV-1 Protease by Structure-Based Computational Screening for Allosteric Inhibitors

Jens Kunze, Nickolay Todoroff, Petra Schneider, Tiago Rodrigues, Tim Geppert, Felix Reisen, Herman Schreuder, Joachim Saas, Gerhard Hessler, Karl-Heinz Baringhaus, Gisbert Schneider [Swiss Federal Institute of Technology (ETH)]

J. Chem. Infor. and Mod. **54**, 987–991, 2014.

We present the discovery of low molecular weight inhibitors of human immunodeficiency virus 1 (HIV-1) protease subtype B that were identified by structure-based virtual screening as ligands of an allosteric surface cavity. For pocket identification and prioritization, we performed a molecular dynamics simulation and observed several flexible, partially transient surface cavities. For one of these presumable ligand-binding pockets that are located in the so-called “hinge region” of the identical protease chains, we computed a receptor-derived pharmacophore model, with which we retrieved fragment-like inhibitors from a screening compound pool.

Macromolecular Crowding Effect upon *In Vitro* Enzyme Kinetics: Mixed Activation–Diffusion Control of the Oxidation of NADH by Pyruvate Catalyzed by Lactate Dehydrogenase

Cristina Balcells, Isabel Pastor [University of Barcelona (UB)], Eudald Vilaseca, Sergio Madurga, Marta Cascante, Francesc Mas

J. Phys. Chem. B., **118**, 4062–4068, 2014.

Enzyme kinetics studies have been usually designed as dilute solution experiments, which differ substantially from *in vivo* conditions. However, cell cytosol is crowded with a high concentration of molecules having different shapes and sizes. The consequences of such crowding in enzymatic reactions remain unclear. The aim of the present study is to understand the effect of macromolecular crowding produced by dextran of different sizes and at diverse concentrations in the well-known reaction of oxidation of NADH by pyruvate catalyzed by L-lactate dehydrogenase (LDH).

Enzyme Catalysis (Cont'd)

Examining Electrostatic Preorganization in Monoamine Oxidases A and B by Structural Comparison and pKa Calculations

Matej Repič, Miha Purg, Robert Vianello, Janez Mavri
[National Institute of Chemistry, Hajdrihova 19]

J. Phys. Chem. B., **118**, 4326–4332, 2014.

Monoamine oxidases (MAO) A and B are important flavoenzymes involved in the metabolism of amine neurotransmitters. Orru et al. (*J. Neural Transm.* 2013, 120, 847–851) recently presented experimental results that have challenged the prevailing assumption that MAO A and MAO B employ an identical catalytic mechanism. We compared the spatial configuration of ionizable groups in both isozymes and estimated the time-averaged electrostatic potential by calculating the pKa values of five active site residues. Superimposition of both experimental structures shows very close overlap and the RMSD in placements of ionizable groups within 16 Å of the reaction center is only 0.847 Å.

Protein-Protein Interactions

Predicting the Impact of Missense Mutations on Protein–Protein Binding Affinity

Minghui Li, Marharyta Petukh, Emil Alexov, Anna R. Panchenko [National Institutes of Health, Bethesda]

J. Chem. Theor. and Comp., **10**, 1770–1780, 2014.

The crucial prerequisite for proper biological function is the protein's ability to establish highly selective interactions with macromolecular partners. A missense mutation that alters the protein binding affinity may cause significant perturbations or complete abolishment of the function, potentially leading to diseases. Here, we report an efficient computational approach for predicting the effect of single and multiple missense mutations on protein–protein binding affinity. It is based on a well-tested simulation protocol for structure minimization, modified MM-PBSA and statistical scoring energy functions with parameters optimized on experimental sets of several thousands of mutations.

Membrane Proteins and Lipid Peptide Interactions

Fast, metadynamics-based method for prediction of the stereochemistry-dependent relative free energies of ligand–receptor interactions

Anita Plazinska, Wojciech Plazinski [J. Haber Institute of Catalysis and Surface Chemistry], Krzysztof Jozwiak

J. Comp. Chem., **35**, 876–882, 2014.

The computational approach applicable for the molecular dynamics (MD)-based techniques is proposed to predict the ligand–protein binding affinities dependent on the ligand stereochemistry. All possible stereoconfigurations are expressed in terms of one set of force-field parameters [stereoconfiguration-independent potential (SIP)], which allows for calculating all relative free energies by only single simulation. SIP can be used for studying diverse, stereoconfiguration-dependent phenomena by means of various computational techniques of enhanced sampling.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Multisurface Adiabatic Reactive Molecular Dynamics

Tibor Nagy[University of Basel], Juvenal Yosa Reyes, and Markus Meuwly

J. Chem. Theor. and Comp., **10**, 1366–1375, 2014.

Adiabatic reactive molecular dynamics (ARMD) simulation method is a surface-crossing algorithm for modeling chemical reactions in classical molecular dynamics simulations using empirical force fields. In the current work, the range of applicability of conventional ARMD is explored, and a new multisurface ARMD (MS-ARMD) method is presented, implemented in CHARMM and applied to the vibrationally induced photodissociation of sulfuric acid (H₂SO₄) in the gas phase. For this, an accurate global potential energy surface (PES) involving 12 H₂SO₄ and 4 H₂O + SO₃ force fields fitted to MP2/6-311G++(2d,2p) reference energies is employed.

Transmembrane Permeation Mechanism of Charged Methyl Guanidine

Yukun Wang, Dan Hu [Shanghai Jiao Tong University], Dongqing Wei

J. Chem. Theor. and Comp., **10**, 1717–1726, 2014.

The mechanism of transmembrane ion permeation is studied using charged methyl guanidine as a model ion. With a widely applied reaction coordinate, our umbrella sampling results reveal a significant finite-size effect in small simulation systems and a serious hysteresis in large systems. Therefore, it is important to re-examine the simulation techniques for studying transmembrane permeation mechanism of ions suggested in previous works. In this work, two novel collective variables are designed to acquire a continuous trajectory of the permeation process and small statistical errors through umbrella sampling.

BP-Dock: A Flexible Docking Scheme for Exploring Protein–Ligand Interactions Based on Unbound Structures

Ashini Bolia, Z. Nevin Gerek, and S. Banu Ozkan [Arizona State University]

J. Chem. Infor. and Mod. **54**, 913–925, 2014.

Molecular docking serves as an important tool in modeling protein–ligand interactions. However, it is still challenging to incorporate overall receptor flexibility, especially backbone flexibility, in docking due to the large conformational space that needs to be sampled. To overcome this problem, we developed a novel flexible docking approach, BP-Dock (Backbone Perturbation-Dock) that can integrate both backbone and side chain conformational changes induced by ligand binding through a multi-scale approach.

Does a More Precise Chemical Description of Protein–Ligand Complexes Lead to More Accurate Prediction of Binding Affinity?

Pedro J. Ballester [University of Cambridge], Adrian Schreyer, Tom L. Blundell

J. Chem. Infor. and Mod. **54**, 944–955, 2014.

Predicting the binding affinities of large sets of diverse molecules against a range of macromolecular targets is an extremely challenging task. The scoring functions that attempt such computational prediction are essential for exploiting and analyzing the outputs of docking, which is in turn an important tool in problems such as structure-based drug design. Classical scoring functions assume a predetermined theory-inspired functional form for the relationship between the variables that describe an experimentally determined or modeled structure of a protein–ligand complex and its binding affinity.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Molecular Simulation of Protein Encapsulation in Vesicle Formation

Bram van Hoof, Albert J. Markvoort [Eindhoven University of Technology], Rutger A. van Santen, and Peter A. J. Hilbers

J. Phys. Chem. B., **118**, 3346–3354, 2014.

Liposomes composed of fatty acids and phospholipids are frequently used as model systems for biological cell membranes. In many applications, the encapsulation of proteins and other biomacromolecules in these liposomes is essential. Intriguingly, the concentration of entrapped material often deviates from that in the solution where the liposomes were formed. While some reports mention reduced concentrations inside the vesicles, concentrations are also reported to be enhanced in other cases. We here investigate the encapsulation of model proteins in spontaneously forming vesicles using molecular dynamics simulations with a coarse grained force field for fatty acids and phospholipids as well as water-soluble and transmembrane proteins.

Anionic Form of Usnic Acid Promotes Lamellar to Nonlamellar Transition in DPPC and DOPC Membranes

Daniela Nadvorný, João Bosco P. da Silva, Roberto D. Lins [Federal University of Pernambuco]

J. Phys. Chem. B., **118**, 3881–3886, 2014.

Usnic acid is a secondary metabolite found in several species of lichens, organisms resulting from the symbiosis between fungi and algae. This compound has been extensively studied because of its pharmacological properties. Despite its potential medicinal importance, it exhibits a high degree of toxicity. The confinement of the usnic acid within liposomes has been investigated as a possibility to reduce its toxicity. In this work, we characterize the interaction of usnic acid in its neutral and anionic states (usniate) with DPPC and DOPC by means of molecular dynamics simulations.

Cholesterol- β_1 AR interaction versus cholesterol- β_2 AR interaction

Xiaohui Cang, Linlin Yang, Jing Yang, Cheng Luo, Mingyue Zheng, Kunqian Yu, Huaiyu Yang, Hualiang Jiang [Chinese Academy of Sciences]

Proteins: Stru. Fun. & Bioinf., **82**, 760–770, 2014.

Two 8- μ s all-atom molecular dynamics simulations have been performed on the two highly homologous G protein-coupled receptor (GPCR) subtypes, β_1 - and β_2 -adrenergic receptors, which were embedded in a lipid bilayer with randomly dispersed cholesterol molecules. During the simulations, cholesterol molecules accumulate to different surface regions of the two receptors, suggesting the subtype specificity of cholesterol- β -adrenergic receptor interaction and providing some clues to the physiological difference of the two subtypes. Meanwhile, comparison between the two receptors in interacting with cholesterol shed some new light on general determinants of cholesterol binding to GPCRs.

Free Energy of Lipid Bilayer Defects Affected by Alzheimer's Disease-Associated Amyloid- β 42 Monomers

Tobias Pobandt, Volker Knecht [Max Planck Institute of Colloids and Interfaces]

J. Phys. Chem. B., **118**, 3507–3516, 2014.

Experimental evidence suggests that the amyloid β -peptide ($A\beta$) associated with Alzheimer's disease strongly disturbs the integrity of lipid bilayers and cell membranes, as a possible origin of the toxicity of this peptide. Here, we have used molecular dynamics simulations to compute the free energy of membrane pores in the presence and absence of $A\beta$. The validation of our approach included the calculation of lipid flip-flop waiting times, which were found to agree well with recent experiments, in contrast with an earlier simulation study that apparently overestimated these waiting times.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Preferred Orientations of Phosphoinositides in Bilayers and Their Implications in Protein Recognition Mechanisms

Emilia L. Wu, Yifei Qi, Kevin C. Song, Jeffery B. Klauda, Wonpil Im [The University of Kansas]

J. Phys. Chem. B., **118**, 4315–4325, 2014.

Phosphoinositides (PIPs), phosphorylated derivatives of phosphatidylinositol (PI), are essential regulatory lipids involved in various cellular processes, including signal transduction, membrane trafficking, and cytoskeletal remodeling. To gain insight into the protein-PIPs recognition process, it is necessary to study the inositol ring orientation (with respect to the membrane) of PIPs with different phosphorylation states. In this study, 8 PIPs (3 PIP, 2 PIP₂, and 3 PIP₃) with different phosphorylation and protonation sites have been separately simulated in two mixed bilayers, which roughly correspond to yeast membranes.

Protein Folding

Observation of Complete Pressure-Jump Protein Refolding in Molecular Dynamics Simulation and Experiment

Yanxin Liu, Maxim B. Prigozhin, Klaus Schulten, Martin Gruebele [University of Illinois]

J. Am. Chem. Soc., 2013, **136**, 4265–4272, 2014.

Density is an easily adjusted variable in molecular dynamics (MD) simulations. Thus, pressure-jump (P-jump)-induced protein refolding, if it could be made fast enough, would be ideally suited for comparison with MD. Although pressure denaturation perturbs secondary structure less than temperature denaturation, protein refolding after a fast P-jump is not necessarily faster than that after a temperature jump. Recent P-jump refolding experiments on the helix bundle λ -repressor have shown evidence of a $<3 \mu\text{s}$ burst phase, but also of a 1.5 ms “slow” phase of refolding, attributed to non-native helical structure frustrating microsecond refolding.

How Quickly Can a β -Hairpin Fold from Its Transition State?

Beatrice N. Markiewicz, Lijiang Yang, Robert M. Culik, Yi Qin Gao, Feng Gai [University of Pennsylvania]

J. Phys. Chem. B., **118**, 3317–3325, 2014.

Understanding the structural nature of the free energy bottleneck(s) encountered in protein folding is essential to elucidating the underlying dynamics and mechanism. For this reason, several techniques, including Φ -value analysis, have previously been developed to infer the structural characteristics of such high free-energy or transition states. Herein we propose that one (or few) appropriately placed backbone and/or side chain cross-linkers, such as disulfides, could be used to populate a thermodynamically accessible conformational state that mimics the folding transition state.

Protein-Nucleic acid Interactions

Conformational changes in DNA-binding proteins: Relationships with precomplex features and contributions to specificity and stability

Munazah Andrabi, Kenji Mizuguchi , Shandar Ahmad
[National Institute of Biomedical Innovation, Osaka]

Both Proteins and DNA undergo conformational changes in order to form functional complexes and also to facilitate interactions with other molecules. These changes have direct implications for the stability and specificity of the complex, as well as the cooperativity of interactions between multiple entities. In this work, we have extensively analyzed conformational changes in DNA-binding proteins by superimposing DNA-bound and unbound pairs of protein structures in a curated database of 90 proteins.

Proteins: Stru. Fun. & Bioinf., **82**, 841–857, 2014.

Nucleic Acids

Comparative analysis of nucleotide translocation through protein nanopores using steered molecular dynamics and an adaptive biasing force

Hugh S. C. Martin, Shantenu Jha , Peter V. Coveney [Centre for Computational Science, London]

J. Comp. Chem., **35**, 692–702, 2014.

The translocation of nucleotide molecules across biological and synthetic nanopores has attracted attention as a next generation technique for sequencing DNA. Computer simulations have the ability to provide atomistic-level insight into important states and processes, delivering a means to develop a fundamental understanding of the translocation event, for example, by extracting the free energy of the process. Even with current supercomputing facilities, the simulation of many-atom systems in fine detail is limited to shorter timescales than the real events they attempt to recreate.

Microsecond simulations of DNA and ion transport in nanopores with novel ion-ion and ion-nucleotides effective potentials

Pablo M. De Biase [University of Calgary], Suren Markosyan ,Sergei Noskov

J. Comp. Chem., **35**, 711–721, 2014.

We developed a novel scheme based on the grand-canonical Monte Carlo/Brownian dynamics simulations and have extended it to studies of ion currents across three nanopores with the potential for single-stranded DNA (ssDNA) sequencing: solid-state nanopore Si3N4, α -hemolysin, and E111N/M113Y/K147N mutant. To describe nucleotide-specific ion dynamics compatible with ssDNA coarse-grained model, we used the inverse Monte Carlo protocol, which maps the relevant ion-nucleotide distribution functions from all-atom molecular dynamics (MD) simulations.

Nuclic Acids (Cont'd)

Improvement of DNA and RNA Sugar Pucker Profiles from Semiempirical Quantum Methods

Ming Huang, Timothy J. Giese, Tai-Sung Lee, Darrin M. York [Rutgers University]

J. Chem. Theor. and Comp., **10**, 1538–1545, 2014.

Neglect of diatomic differential overlap (NDDO) and self-consistent density-functional tight-binding (SCC-DFTB) semiempirical models commonly employed in combined quantum mechanical/molecular mechanical simulations fail to adequately describe the deoxyribose and ribose sugar ring puckers. This failure limits the application of these methods to RNA and DNA systems. In this work, we provide benchmark ab initio gas-phase two-dimensional potential energy scans of the RNA and DNA sugar puckering. The benchmark calculations are compared with semiempirical models.

Surfaces, Catalysts, and Materials Subjects

Solubilization in Mixed Micelles Studied by Molecular Dynamics Simulations and COSMOmic

Sandra Storm, Sven Jakobtorweihen [Hamburg University of Technology], Irina Smirnova

J. Phys. Chem. B., **118**, 3593–3604, 2014.

This work is focused on molecular simulations of phase equilibria in mixed surfactant systems, because mixtures of different types of surfactants (nonionic or ionic) in aqueous solution can change the partition behavior of solutes tremendously. The extension of COSMO-RS for anisotropic phases, named COSMOmic, is computationally efficient and can be used as a screening tool for finding adequate surfactant systems for a specific extraction task. However, it needs micellar structures as an input. Therefore, molecular dynamics (MD) simulations of the self-assembly of pure Brij35 (polyethylene glycol dodecyl ether) and mixtures either with CTAB (cetyltrimethyl ammonium bromide) or SDS (sodium dodecyl sulfate) at different concentrations are performed.

Molecular Dynamics Simulations of Sodium Dodecyl Sulfate Micelles in Water—The Effect of the Force Field

Xueming Tang, Peter H. Koenig, Ronald G. Larson [University of Michigan]

J. Phys. Chem. B., **118**, 3864–3880, 2014.

Molecular dynamic (MD) simulations of preassembled sodium dodecyl sulfate (SDS) micelles are carried out using three versions of GROMOS, as well as CHARMM36, OPLS-AA, and OPLS-UA force fields at different aggregation numbers and box sizes. The differences among force fields have little effect on the overall micelle structure of small aggregates of size 60 or 100, but for micelles of an aggregation number of 300 or higher, bicelle structures with ordered tails, rather than the more realistic rodlike or cylindrical micelles with disordered tails, occur when using versions of GROMOS45A3 or the OPLS-AA force fields that are adapted to model the sulfate head group atoms using methods given in the literature.

Surfaces, Catalysts, and Material Subjects (Cont'd)

Structural Properties of CHAPS Micelles, Studied by Molecular Dynamics Simulations

Fernando E. Herrera [Universidad Nacional del Litoral (UNL)], A. Sergio Garay, Daniel E. Rodrigues

J. Phys. Chem. B., **118**, 3912–3921, 2014.

Detergents are essential tools to study biological membranes, and they are frequently used to solubilize lipids and integral membrane proteins. Particularly the nondenaturing zwitterionic detergent usually named CHAPS was designed for membrane biochemistry and integrates the characteristics of the sulfobetaine-type detergents and bile salts. Despite the available experimental data little is known about the molecular structure of its micelles. In this work, molecular dynamics simulations were performed to study the aggregation in micelles of several numbers of CHAPS (≤ 18) starting from a homogeneous water dilution.

2. METHODOLOGY

Quantitative Structure-Activity Relations

A New Approach to Radial Basis Function Approximation and Its Application to QSAR

Alexey V. Zakharov, Megan L. Peach [National Institutes of Health, DHHS, NCI-Frederick], Markus Sitzmann, and Marc C. Nicklaus

J. Chem. Infor. and Mod. **54**, 713–719, 2014.

We describe a novel approach to RBF approximation, which combines two new elements: (1) linear radial basis functions and (2) weighting the model by each descriptor's contribution. Linear radial basis functions allow one to achieve more accurate predictions for diverse data sets. Taking into account the contribution of each descriptor produces more accurate similarity values used for model development. The method was validated on 14 public data sets comprising nine physicochemical properties and five toxicity endpoints.

Merging Applicability Domains for in Silico Assessment of Chemical Mutagenicity

Ruifeng Liu, Anders Wallqvist [U.S. Army Medical Research and Materiel Command]

J. Chem. Infor. and Mod. **54**, 793–800, 2014.

Using a benchmark Ames mutagenicity data set, we evaluated the performance of molecular fingerprints as descriptors for developing quantitative structure–activity relationship (QSAR) models and defining applicability domains with two machine-learning methods: random forest (RF) and variable nearest neighbor (v-NN). The two methods focus on complementary aspects of chemical mutagenicity and use different characteristics of the molecular fingerprints to achieve high levels of prediction accuracies.

Quantitative Structure-Activity Relations (Cont'd)

Choosing Feature Selection and Learning Algorithms in QSAR

Martin Eklund, Ulf Norinder, Scott Boyer, Lars Carlsson [Uppsala University]

J.Chem. Infor. and Mod. **54**, 837–843, 2014.

Feature selection is an important part of contemporary QSAR analysis. In a recently published paper, we investigated the performance of different feature selection methods in a large number of in silico experiments conducted using real QSAR datasets. In this report we extend our work from the previous investigation by using four different feature selection methods (wrapper, ReliefF, MARS, and elastic nets), together with eight learners (MARS, elastic net, random forest, SVM, neural networks, multiple linear regression, PLS, kNN) in an empirical investigation to address this question.

Hsp90 Inhibitors, Part 1: Definition of 3-D QSAutogrid/R Models as a Tool for Virtual Screening

Flavio Ballante, Antonia Caroli, Richard B. Wickersham, III, and Rino Ragno [Sapienza Università di Roma]

J.Chem. Infor. and Mod. **54**, 956–969, 2014.

The multichaperone heat shock protein (Hsp) 90 complex mediates the maturation and stability of a variety of oncogenic signaling proteins. For this reason, Hsp90 has emerged as a promising target for anticancer drug development. Herein, we describe a complete computational procedure for building several 3-D QSAR models used as a ligand-based (LB) component of a comprehensive ligand-based (LB) and structure-based (SB) virtual screening (VS) protocol to identify novel molecular scaffolds of Hsp90 inhibitors.

Potentials and Parameters

Parameterization of DFTB3/3OB for Sulfur and Phosphorus for Chemical and Biological Applications

Michael Gaus, Xiya Lu, Marcus Elstner, Qiang Cui [University Avenue, Madison]

J. Chem. Theor. and Comp. **10**, 1518–1537, 2014.

We report the parametrization of the approximate density functional tight binding method, DFTB3, for sulfur and phosphorus. The parametrization is done in a framework consistent with our previous 3OB set established for O, N, C, and H, thus the resulting parameters can be used to describe a broad set of organic and biologically relevant molecules. The 3d orbitals are included in the parametrization, and the electronic parameters are chosen to minimize errors in the atomization energies.

Update to the General Amber Force Field for Small Solutes with an Emphasis on Free Energies of Hydration

Joakim P. M. Jämbeck, Alexander P. Lyubartsev [Stockholm University]

J. Phys. Chem. B., **118**, 3793–3804, 2014.

An approach to a straightforward reparametrization of the general AMBER force field (GAFF) for small organic solutes and druglike compounds is presented. The parametrization is based on specific pair interactions between the solvent and the solute, namely, the interactions between the constituting atoms of the solute and the oxygen of water were tuned in order to reproduce experimental hydration free energies for small model compounds. The key of the parametrization was to abandon the Lorentz–Berthelot combination rules for the van der Waals interactions.

Molecular Dynamics

Protocol To Make Protein NMR Structures Amenable to Stable Long Time Scale Molecular Dynamics Simulations

Da-Wei Li , Rafael Brüschweiler [Florida State University]

J. Chem. Theor. and Comp, **10**, 1781–1787, 2014.

A robust protocol for the treatment of NMR protein structures is presented that makes them amenable to long time scale molecular dynamics (MD) simulations that are stable. The protocol embeds an NMR structure in a native low energy region of the recently developed ff99SB_φψ(g24;CS) molecular mechanics force field. Extended MD trajectories that start from these structures show good consistency with proton-proton nuclear Overhauser effect data, and they reproduce NMR chemical shift data better than the original NMR structures as is demonstrated for four protein systems.

Mapping the intramolecular signal transduction of G-protein coupled receptors

Yoonji Lee, Sun Choi[Ewha Womans University], Changbong Hyeon

Proteins: Stru. Fun. & Bioinf., **82**, 727–743, 2014.

G-protein coupled receptors (GPCRs), a major gatekeeper of extracellular signals on plasma membrane, are unarguably one of the most important therapeutic targets. Given the recent discoveries of allosteric modulations, an allosteric wiring diagram of intramolecular signal transductions would be of great use to glean the mechanism of receptor regulation. Here, by evaluating betweenness centrality (C_B) of each residue, we calculate maps of information flow in GPCRs and identify key residues for signal transductions and their pathways.

Evaluation of Enhanced Sampling Provided by Accelerated Molecular Dynamics with Hamiltonian Replica Exchange Methods

Daniel R. Roe, Christina Bergonzo, and Thomas E. Cheatham, III [University of Utah]

J. Phys. Chem. B., **118**, 3543–3552, 2014.

In this work, we study the enhanced sampling of the RNA tetranucleotide r(GACC) provided by H-REMD combined with accelerated molecular dynamics (aMD), where a boosting potential is applied to torsions, and compare this to the enhanced sampling provided by H-REMD in which torsion potential barrier heights are scaled down to lower force constants. We show that H-REMD and multidimensional REMD (M-REMD) combined with aMD does indeed enhance sampling for r(GACC), and that the addition of the temperature dimension in the M-REMD simulations is necessary to efficiently sample rare conformations.

QM and QM/MM

Multiscale Free Energy Simulations: An Efficient Method for Connecting Classical MD Simulations to QM or QM/MM Free Energies Using Non-Boltzmann Bennett Reweighting Schemes

Gerhard König, Phillip S. Hudson, Stefan Boresch, H. Lee Woodcock [University of South Florida]

J. Chem. Theor. and Comp., **10**, 1406–1419, 2014.

The reliability of free energy simulations (FES) is limited by two factors: (a) the need for correct sampling and (b) the accuracy of the computational method employed. Classical methods (e.g., force fields) are typically used for FES and present a myriad of challenges, with parametrization being a principle one. On the other hand, parameter-free quantum mechanical (QM) methods tend to be too computationally expensive for adequate sampling. One widely used approach is a combination of methods, where the free energy difference between the two end states is computed by, e.g., molecular mechanics (MM), and the end states are corrected by more accurate methods, such as QM or hybrid QM/MM techniques.

Geometry Optimization in Polarizable QM/MM Models: The Induced Dipole Formulation

Stefano Caprasecca, Sandro Jurinovich, Lucas Viani, Carles Curutchet, Benedetta Mennucci [University of Pisa]

J. Chem. Theor. and Comp., **10**, 1588–1598, 2014.

We present the mathematical derivation and the computational implementation of the analytical geometry derivatives for a polarizable QM/MM model (QM/MMPol). In the adopted QM/MMPol model, the focused part is treated at QM level of theory, while the remaining part (the environment) is described classically as a set of fixed charges and induced dipoles. The implementation is performed within the ONIOM procedure, resulting in a polarizable embedding scheme, which can be applied to solvated and embedded systems and combined with different polarizable force fields available in the literature.

Simple Link Atom Saccharide Hybrid (SLASH) Treatment for Glycosidic Bonds at the QM/MM Boundary

Werner Crous, Martin J. Field, Kevin J. Naidoo [University of Cape Town]

J. Chem. Theor. and Comp., **10**, 1727–1738, 2014.

We investigated link atom approaches for treating the polar C–O bond with particular reference to the glycosidic bond found in complex carbohydrates. We show that cutting this bond after the oxygen in the QM region and saturating the QM system with a hydrogen link atom leads to greater conformational and configurational accuracy at the boundary compared with cutting the bond before oxygen and saturating the QM system with a halogen link atom to represent the oxygen. Furthermore, we find that balancing the MM atom charges and redistributing the boundary atom charges at the QM/MM boundary minimizes the effect of the link atom, both energetically and structurally.

Toward QM/MM Simulation of Enzymatic Reactions with the Drude Oscillator Polarizable Force Field

Eliot Boulanger, Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Chem. Theor. and Comp., **10**, 1795–1809, 2014.

The polarization of the environment can influence the results from hybrid QM/MM simulations of enzymatic reactions. In this article, we address several technical aspects in the development of polarizable QM/MM embedding using the Drude Oscillator (DO) force field. We propose a stable and converging update of the DO polarization state for geometry optimizations and a suitable treatment of the QM/MM-DO boundary when the QM and MM regions are separated by cutting through a covalent bond.

QM and QM/MM (Cont'd)

Potency Prediction of β -Secretase (BACE-1) Inhibitors Using Density Functional Methods

Katarina Roos [AstraZeneca R&D Mölndal], Jenny Viklund, Johan Meuller, Karin Kaspersson, Mats Svensson

J.Chem. Infor. and Mod. **54**, 818–825, 2014.

Scoring potency is a main challenge for structure based drug design. Inductive effects of subtle variations in the ligand are not possible to accurately predict by classical computational chemistry methods. In this study, the problem of predicting potency of ligands with electronic variations participating in key interactions with the protein was addressed. The potency was predicted for a large set of cyclic amidine and guanidine cores extracted from β -secretase (BACE-1) inhibitors.

Capping Amyloid β -Sheets of the Tau-Amyloid Structure VQIVYK with Hexapeptides Designed To Arrest Growth. An ONIOM and Density Functional Theory Study

Joshua A. Plumley, Jorge Ali-Torres, Gabor Pohl, J. J. Dannenberg [City University of New York]

J. Phys. Chem. B., **118**, 3326–3334, 2014.

We delineate and explore several design principles (H-bonding in the side chains, using antiparallel interactions on the growing edge of a parallel sheet, using all-D residues to form rippled interactions at the edge of the sheet, and replacing the H-bond donor N–H's that inhibit further growth) that can be used individually and in combination to design such peptides that will have a greater affinity for binding to the parallel β -sheet of acetyl-VQIVYK-NHCH₃ than the natural sequence and will prevent another strand from binding to the sheet, thus providing a cap to the growing sheet that arrests further growth.

Mechanistic Insights into Metal (Pd²⁺, Co²⁺, and Zn²⁺)– β -Cyclodextrin Catalyzed Peptide Hydrolysis: A QM/MM Approach

Tingting Zhang, Xiaoxia Zhu, Rajeev Prabhakar [University of Miami]

J. Phys. Chem. B., **118**, 4106–4114, 2014.

In this study, mechanistic insights into the hydrolysis of an extremely stable tertiary peptide bond (Ser–Pro) in the Ser-Pro-Phe sequence by an artificial enzyme, metal (Pd²⁺, Co²⁺, or Zn²⁺)– β -cyclodextrin (CD) complex, have been provided. In particular, the exact reaction mechanism, the location of CD (number of –CH₂ groups downstream from the metal center), conformation of CD (primary or secondary rim of CD facing the substrate), the number of CD (one or two), and the optimum metal ion (Pd²⁺, Co²⁺, or Zn²⁺) have been suggested using a state-of-the-art hybrid quantum mechanics/molecular mechanics (QM/MM: B3LYP/Amber) approach.

Ligand Docking

Protein-Triggered Supramolecular Disassembly: Insights Based on Variations in Ligand Location in Amphiphilic Dendrons

Diego Amado Torres, Matteo Garzoni, Ayyagari V. Subrahmanyam, Giovanni M. Pavan [University of Applied Science of Southern Switzerland], S. Thayumanavan

J. Am. Chem. Soc., 2013, **136**, 5385–5399, 2014.

We use monodisperse dendrons that allow control over functional group presentation to investigate the influence of the location of a ligand on protein-induced disassembly and release of encapsulated small molecules. Based on both experiments and molecular dynamics simulations, we demonstrate that ligand location greatly influences release of guest molecules from the dendron-based supramolecular assembly. We show that a ligand moiety grafted to the dendron periphery is more accessible for the target protein in aqueous solution.

Ligand Docking (Cont'd)

Mechanism of Stapled Peptide Binding to MDM2: Possible Consequences for Peptide Design

Adelene Y. L. Sim, Thomas Joseph, David P. Lane, Chandra Verma [National University of Singapore]

J. Chem. Theor. and Comp., **10**, 1753–1761, 2014.

MDM2 is a negative regulator of p53. The N terminal domain of MDM2 interacts with a helical region of the transcriptional activation domain of p53. Stapled peptides have been designed to mimic this interaction, in order to inhibit p53-MDM2 binding and thereby activate the p53 response. Here, we studied how the helical segment of p53 or a stapled peptide (re)binds to MDM2 as it is systematically displaced from the MDM2 binding pocket. Depending on its sequence, presence of staple, and/or a C-terminal tail, the peptide approaches MDM2 differently and not exclusively via the crack propagation mechanism proposed previously for p53.

Application of Docking and QM/MM-GBSA Rescoring to Screen for Novel Myt1 Kinase Inhibitors

Kanin Wichapong, Alexander Rohe, Charlott Platzer, Inna Slynko, Frank Erdmann, Matthias Schmidt, Wolfgang Sippl [Martin-Luther-University Halle-Wittenberg]

J.Chem. Infor. and Mod. **54**, 881–893, 2014.

Identification of compounds that can bind to a target protein with high affinity is a nontrivial task in structure-based drug design. Several approaches ranging from simple scoring methods to more computationally demanding methods are usually applied for this purpose. In the current work, we used ligand docking in combination with QM/MM-GBSA, MM-GBSA, and MM-PBSA rescoring to discriminate between active and inactive Myt1 kinase inhibitors. Results show that QM/MM-GBSA rescoring performs better than normal docking scores or MM-GBSA rescoring in classifying active and inactive inhibitors.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 50, April, 2014.

- 1-9 **In silico investigation of medicinal spectrum of imidazo-azines from the perspective of multitarget screening against malaria, tuberculosis and Chagas disease** ,Manoj Kumar, Barnita Makhal, Vinod Kumar Gupta, Anuj Sharma [Indian Institute of Technology Roorkee]

See Applications / Medicinal Chemmistry and Drug Design.

- 10-15 **Enhanced stability of a naringenin/2,6-dimethyl β -cyclodextrin inclusion complex: Molecular dynamics and free energy calculations based on MM- and QM-PBSA/GBSA** ,Waratchada Sangpheak, Wasinee Khuntawee, Peter Wolschann, Piamsook Pongsawasdi, Thanyada Rungrotmongkol [Chulalongkorn University]

See Applications / Ligand Binding.

- 16-34 **Designing of multi-targeted molecules using combination of molecular screening and in silico drug cardiotoxicity prediction approaches** ,Birce Buturak, Serdar Durdagi, Sergei Y. Noskov, A. Tugba Ozal Ildeniz [Kadir Has University]

See Applications / Ligand Binding.

- 35-43 **GCMC simulations of CO₂ adsorption on zeolite-supported Ir₄ clusters** ,Daniel Smykowski [Wrocław University of Technology], Bartłomiej Szyja, Jerzy Szczygieł

We have studied the adsorption of CO₂ molecules inside the pores of faujasite zeolite and evaluated the influence of the Ir₄ clusters on the intensity of the adsorption. The force field designed for CO₂ adsorption in zeolites has been extended with the parameters for the CO₂/Ir₄ interactions, taking the Density Functional Theory (DFT) energies as a reference.

- 44-49 **VCMM: A visual tool for continuum molecular modeling** ,Shiyang Bai, Benzhuo Lu [Chinese Academy of Sciences]

See Applications / Bioinformatics.

Journal of Computational Chemistry, 35 (9), April, 2014.

- 683–691 **Implicit and explicit solvent models for modeling a bifunctional arene ruthenium hydrogen-storage catalyst: A classical and ab initio molecular simulation study** ,Sateesh Bandaru, Niall J. English [University College Dublin] , J. M. D. MacElroy

Classical and ab initio, density functional theory- and semiempirical-based molecular simulation, including molecular dynamics, have been carried out to compare and contrast the effect of explicit and implicit solvation representation of tetrahydrofuran (THF) solvent on the structural, energetic, and dynamical properties of a novel bifunctional arene ruthenium catalyst embedded therein.

- 692–702 **Comparative analysis of nucleotide translocation through protein nanopores using steered molecular dynamics and an adaptive biasing force** ,Hugh S. C. Martin, Shantenu Jha , Peter V. Coveney [Centre for Computational Science, London]

See Applications / Nucleic Acids.

- 703–710 **The reliability of DFT methods to predict electronic structures and minimum energy crossing point for [FeIVO](OH)₂ models: A comparison study with MCQDPT method** ,Kun Liu [Tianjin Normal University], Yu-Xue Li, Jia-Ling Su , Bin Wang

In order to test the reliability of DFT methods for calculating electronic structures of [FeIVO] system, detailed calculations of [FeIVO](OH)₂models were performed for several low-energy states using multiconfiguration quasidegenerate perturbation theory (MCQDPT) as well as DFT-based methods.

- 711–721 **Microsecond simulations of DNA and ion transport in nanopores with novel ion–ion and ion–nucleotides effective potentials** ,Pablo M. De Biase [University of Calgary], Suren Markosyan ,Sergei Noskov

See Applications / Nucleic Acids.

- 722–736 **The effect of the intermolecular potential formulation on the state-selected energy exchange rate coefficients in N₂–N₂ collisions** ,Alexander Kurnosov, Mario Cacciatore, Antonio Laganà, Fernando Pirani, Massimiliano Bartolomei ,Ernesto Garcia [Universidad del País Vasco (UPV/EHU)]

The rate coefficients for N₂–N₂ collision-induced vibrational energy exchange (important for the enhancement of several modern innovative technologies) have been computed over a wide range of temperature.

- 737–747 **Accessing the applicability of polarized protein-specific charge in linear interaction energy analysis** ,Xiangyu Jia, Juan Zeng, John Z. H. Zhang , Ye Mei [East China Normal University]

The reliability of the linear interaction energy (LIE) depends on the atomic charge model used to delineate the Coulomb interaction between the ligand and its environment. In this work, the polarized protein-specific charge (PPC) implementing a recently proposed fitting scheme has been examined in the LIE calculations of the binding affinities for avidin and β -secretase binding complexes.

- 748–755 **Continuous symmetry measures for complex symmetry group** ,Chaim Dryzun [The Open University of Israel]

Symmetry is a fundamental property of nature, used extensively in physics, chemistry, and biology. The Continuous symmetry measures (CSM) is a method for estimating the deviation of a given system from having a certain perfect symmetry, which enables us to formulate quantitative relation between symmetry and other physical properties. Here, we present a methodology for calculating the CSM of any complex point group, including the dihedral, tetrahedral, octahedral, and icosahedral symmetry groups.

- 756–764 **Integrating open-source software applications to build molecular dynamics systems** ,Bruce M. Allen [University of Denver], Paul K. Predecki, Maciej Kumosa

See Applications / Bioinformatics.

Journal of Computational Chemistry, 35 (10), April, 2014.

- 765–771 **Efficient computation of root mean square deviations under rigid transformations** ,Anna K. Hildebrandt [Saarland University], Matthias Dietzen, Thomas Lengauer, Hans-Peter Lenhof, Ernst Althaus ,Andreas Hildebrandt

The computation of root mean square deviations (RMSD) is an important step in many bioinformatics applications. If approached naively, each RMSD computation takes time linear in the number of atoms. In addition, a careful implementation is required to achieve numerical stability, which further increases runtimes.

- 772–775 **LUMPAC lanthanide luminescence software: Efficient and user friendly** ,José Diogo L. Dutra, Thiago D. Bispo , Ricardo O. Freire [Pople Computational Chemistry Laboratory, UFS]

In this study, we will be presenting LUMPAC (LUMinescence PACKage), which was developed with the objective of making possible the theoretical study of lanthanide-based luminescent systems

- 776–788 **Fully atomistic molecular-mechanical model of liquid alkane oils: Computational validation** ,Tsvetan K. Zahariev, Radomir I. Slavchov, Alia V. Tadjer, Anela N. Ivanova [University of Sofia]

Fully atomistic molecular dynamics simulations were performed on liquid n-pentane, n-hexane, and n-heptane to derive an atomistic model for middle-chain-length alkanes. All simulations were based on existing molecular-mechanical parameters for alkanes.

- 789–801 **A polarizable empirical force field for molecular dynamics simulation of liquid hydrocarbons** ,Oliwia M. Szklarczyk, Stephan J. Bachmann , Wilfred F. van Gunsteren [Swiss Federal Institute of Technology ETH]

Electronic polarizability is usually treated implicitly in molecular simulations, which may lead to imprecise or even erroneous molecular behavior in spatially electronically inhomogeneous regions of systems such as proteins, membranes, interfaces between compounds, or mixtures of solvents. In this work, we report a polarizable COS model for cyclohexane, as this molecule is a widely used solvent, and for linear alkanes,

which are also used as solvents, and are the precursors of lipids, amino acid side chains, carbohydrates, or nucleic acid backbones.

- 802–808 **The total Position Spread in mixed-valence compounds: A study on the H4⁺ model system**, Gian Luigi Bendazzoli, Muammar El Khatib, Stefano Evangelisti [Université de Toulouse et CNRS], Thierry Leininger

The behavior of the Total Position Spread (TPS) tensor, which is the second moment cumulant of the total position operator, is investigated in the case of a mixed-valence model system. The system consists of two H₂ molecules placed at a distance D.

- 809–819 **Predicting adsorption enthalpies on silicalite and HZSM-5: A benchmark study on DFT strategies addressing dispersion interactions**, Cheng-chau Chiu, Georgi N. Vayssilov, Alexander Genest, Armando Borgna, Notker Rösch [Technische Universität München]

We evaluated the accuracy of periodic density functional calculations for adsorption enthalpies of water, alkanes, and alcohols in silicalite and HZSM-5 zeolites using a gradient-corrected density functional with empirical dispersion corrections (PBE-D) as well as a nonlocal correlation functional (vdW-DF2).

- 820–828 **Properties of atoms in electronically excited molecules within the formalism of TDDFT**, Eric Iván Sánchez-Flores, Rodrigo Chávez-Calvillo, Todd A. Keith, Gabriel Cuevas, Tomás Rocha-Rinza [Ciudad Universitaria], Fernando Cortés-Guzmán

The topological analysis of the electron density for electronic excited states under the formalism of the quantum theory of atoms in molecules using time-dependent density functional theory (TDDFT) is presented.

Journal of Computational Chemistry, 35 (11), April, 2014.

- 829–838 **Significant nonlinear-optical switching capacity in atomic clusters built from silicon and lithium: A combined ab initio and density functional study**, Panagiotis Karamanis [IPREM Institut des Sciences Analytiques et de Physico-chimie pour l'Environnement et les Matériaux (IPREM) UMR 5254], Nicolás Otero, Claude Pouchan, Juan José Torres, William Tiznado, Aggelos Avramopoulos Manthos G. Papadopoulos

Starting from a hypothetical but fundamental charge/discharge sequence, the topic of nonlinear optical switching in atomic clusters built from silicon and alkali metals is opened up. The outcomes presented in this work, obtained with ab initio methods of exceptional predictive capabilities, offer strong evidences that sizable hyperpolarizability contrasts between neutral and charged alkali metal doped cluster forms might be simultaneously accomplished.

- 839–846 **The cyclic cluster model at hartree–fock level**, Michael F. Peintinger [University of Bonn], Thomas Bredow

We present the implementation of the cyclic cluster model (CCM) formalism at the Hartree–Fock (HF) level. In contrast to other periodic models, the CCM is a Γ -point approach. Integration is carried out in real space within a finite interaction area determined by the size and the shape of the cluster that corresponds to a supercell of the solid, surface, or polymer.

- 847–853 **Quantum-chemical analyses of aromaticity, UV spectra, and NMR chemical shifts in plumbacyclopentadienylidenes stabilized by Lewis bases** ,Toshiaki Kawamura, Minoru Abe, Masaichi Saito, Masahiko Hada [Tokyo Metropolitan University]

We carried out a series of zeroth-order regular approximation (ZORA)-density functional theory (DFT) and ZORA-time-dependent (TD)-DFT calculations for molecular geometries, NMR chemical shifts, nucleus-independent chemical shifts (NICS), and electronic transition energies of plumbacyclopentadienylidenes stabilized by several Lewis bases, (Ph)₂(tBuMe₂Si)₂C₄PbL₁L₂ (L₁, L₂ = tetrahydrofuran, Pyridine, N-heterocyclic carbene), and their model molecules.

- 854–864 **Maxima of $|\Psi|^2$: A connection between quantum mechanics and Lewis structures** ,Arne Lüchow [RWTH Aachen University]

The maxima of squared electronic wave functions are analyzed for a number of small molecules. They are in principle observables and show considerable chemical insight from first principles.

- 865–875 **Design of a reaction field using a linear-combination-based isotropic periodic sum method** ,Kazuaki Z. Takahashi [Keio University]

In our previous study (Takahashi et al., J. Chem. Theory Comput. 2012, 8, 4503), we developed the linear-combination-based isotropic periodic sum (LIPS) method. To demonstrate this, in the present work, a novel reaction field of the LIPS method was developed. The novel reaction field was labeled LIPS-SW, because it provides an interaction potential function with a shape that resembles that of the switch function method.

- 876–882 **Fast, metadynamics-based method for prediction of the stereochemistry-dependent relative free energies of ligand–receptor interactions** ,Anita Plazinska, Wojciech Plazinski [J. Haber Institute of Catalysis and Surface Chemistry] , Krzysztof Jozwiak

See Applications / membrane proteins and lipid- peptide Interaction.

- 883–890 **A two-step reaction scheme leading to singlet carbene species that can be detected under matrix conditions for the reaction of Zr(3F) with either CH₃F or CH₃CN** ,Ana E. Torres, Guadalupe Castro, Ricardo Pablo-Pedro , Fernando Colmenares [Massachusetts Institute of Technology]

The results obtained from CASSCF-MRMP2 calculations are used to rationalize the singlet complexes detected under matrix-isolation conditions for the reactions of laser-ablated Zr(3F) atoms with the CH₃F and CH₃CN molecules, without invoking intersystem crossings between electronic states with different multiplicities.

Journal of Molecular Modeling, 20 (4), April, 2014.

- 2216 **Microhydration of caesium compounds: Cs, CsOH, CsI and Cs₂I₂ complexes with one to three H₂O molecules of nuclear safety interest** ,Mária Sudolská [Comenius University], Laurent Cantrel, Ivan Černušák

Structure and thermodynamic properties (standard enthalpies of formation and Gibbs free energies) of hydrated caesium species of nuclear safety interest, Cs, CsOH, CsI and its dimer Cs₂I₂, with one up to three water molecules, are calculated to assess their possible existence in severe accident occurring to a pressurized water reactor.

- 2215 **Density functional theory study of mixed-phase TiO₂: heterostructures and electronic properties**, Wei-Kun Li, Peijun Hu, Guanzhong Lu [East China University of Science and Technology], Xue-Qing Gong

In this work, density functional theory calculations have been performed to study the geometric, electronic, and energetic properties of two-phase TiO₂ composites built by joining two single-phase TiO₂ slabs, aiming at verifying possible improvement of the photo-activities of the composites through phase separation of excitons.

- 2214 **Adsorption of HCN on reduced graphene oxides: a first-principles study**, Meilian Zhao, Feng Yang, Ying Xue, Dan Xiao [Sichuan University], Yong Guo

The interactions between HCN and reduced graphene oxides (rGO) are investigated using first-principles calculations with M06-2X functional. The results show that the adsorption of HCN on rGO is generally stronger than that on graphene, which is due to the presence of the active defect sites in rGO, such as the hydroxyl, epoxide, and carboxyl functional groups and even the carbon atom near these groups.

- 2212 **Molecular dynamics investigation of Helicobacter pylori chemotactic protein CheY1 and two mutants**, Ahmet Yildirim, Mustafa Tekpinar, Tsjerk A. Wassenaar [University of Erlangen-Nürnberg]

See Applications / Ligand Binding.

- 2211 **Theoretical study on the mechanisms of polyethylene electrical breakdown strength increment by the addition of voltage stabilizers**, Hui Zhang, Hong Zhao, Xuan Wang, Yan Shang, Baozhong Han [Harbin University of Science and Technology], Zesheng Li

A theoretical investigation on the mechanisms of electrical breakdown strength increment of polyethylene at the atomic and molecular levels is accomplished. The addition of aromatic carbonyl and carboxyl compounds as voltage stabilizers may increase the electrical breakdown strength of polyethylene.

- 2209 **Effect of stepwise microhydration on the guanidinium••• π interaction**, Ana A. Rodríguez-Sanz, Enrique M. Cabaleiro-Lago [Universidade de Santiago de Compostela], Jesús Rodríguez-Otero

The characteristics of the interaction of microhydrated guanidinium cation with the aromatic moieties present in the aromatic amino acids side chains have been studied by means of computational methods. The most stable minima found for non-hydrated complexes correspond in all cases to structures with guanidinium oriented toward the ring and interacting by means of N-H••• π hydrogen bonds.

- 2207 **Understanding the high reactivity of triazolinediones in Diels-Alder reactions. A DFT study**, María A. Fernández-Herrera [Benemérita Universidad Autónoma de Puebla], Claudia Zavala-Oseguera, José Luis Cabellos, Jesús Sandoval-Ramírez, Luis R. Domingo, Gabriel Merino

The participation of 4-substituted-1,2,4-triazoline-3,5-diones (TADs) in Diels-Alder reactions toward a series of dienes is studied at the M05-2X/6-31+G(d,p) level. These reactions show very low activation energies and complete endo selectivity, in agreement with the experimental data.

- 2206 **Zinc-, cadmium-, and mercury-containing one-dimensional tetraphenylporphyrin arrays: a DFT study**, Ulises Jiménez Castillo, Ana E. Torres, Serguei Fomine [Universidad Nacional Autónoma de México]

- Metal-free, Zn-, Cd-, and Hg-containing one-dimensional tetraphenylporphyrin arrays containing up to eight repeat units were modeled at the PBE/def2-SVP level of theory with D3 empirical dispersion correction. Two different configurations—face to face (F) and parallel displaced (P)—were detected, the latter being the most stable for all types of nanoarrays.
- 2205 **Theoretical studies on benzo[1,2,4]triazine-based high-energy materials** ,Hari Ji Singh[DDU Gorakhpur University], Manish Kumar Upadhyay, Soumitra Kumar Sengupta
- Density functional theory calculations of 13 aminonitro compounds based on the benzo[1,2,4]triazine fused-ring system were performed. The geometries of all 13 species were optimized at the B3LYP/6-31G(d) level of theory.
- 2204 **Computational studies on the energetic properties of polynitroxanthines** ,Mei Li, Hang Xu [Henan University of Science and Technology], Fengmin Wu
- Density function theory calculations were performed to find comprehensive relationships between the structures and properties of a series of highly energetic polynitroxanthines. The isodesmic reaction method was employed to estimate the gas-phase heat of formation.
- 2203 **CNXeCl and CNXeBr species as halogen bond donors: a quantum chemical study on the structure, properties, and nature of halogen...nitrogen interactions** ,Mehdi D. Esrafil [University of Maragheh], Parisa Juyban
- In the present study, strength and characteristic of halogen bond interactions between CNXeY and NCZ molecules are investigated, where Y = Cl, Br and Z = H, CN, F, OH, CH₃, OCH₃, NH₂. MP2/aug-cc-pVTZ calculations indicate that the interaction energies for CNXeY...NCZ complexes lie in the range between -1.0 and -3.1 kcal mol⁻¹.
- 2202 **DFT study of the mechanism of the reaction of aminoguanidine with methylglyoxal** Christian Solís-Calero, Joaquín Ortega-Castro[Universitat de les Illes Balears], Alfonso Hernández-Laguna, Francisco Muñoz
- We have studied the mechanism of the reaction between aminoguanidine (AG) and methylglyoxal (MG) by carrying out Dmol3/DFT calculations, obtaining intermediates, transition-state structures, and free-energy profiles for all of the elementary steps of the reaction.
- 2201 **Structures and electro-optical properties of Möbius [n]Cyclacenes[13–18]: a theoretical study** ,Ying Gao, Hong-Liang Xu [Northeast Normal University], Rong-Lin Zhong, Shi-Ling Sun, Zhong-Min Su
- Due to the unusual properties of the Möbius cyclacenes (MC) such as π electrons, MC has drawn the extensive attention of scientists. In the present work, six [n]MC (n = 13–18, n is the number of benzenoid rings) were systematically investigated to explore the size-dependent effects on structures, electro-optical properties, and frontier molecule orbits (FMO).
- 2200 **Host-guest complexes of calix[4]tubes - prediction of ion selectivity by quantum chemical calculations VI** ,Svetlana Begel, Ralph Puchta [University of Erlangen-Nürnberg], Rudi van Eldik

See Applications / Host-Guest System.

- 2199 **A study of the rotational barriers for some organic compounds using the G3 and G3CEP theories** ,Douglas Henrique Pereira, Lucas Colucci Ducati, Roberto Rittner, Rogério Custodio [Universidade Estadual de Campinas]

The G3, G3CEP, MP4, MP4CEP, QCISD(T), and QCISD(T)CEP methods were applied to study 43 internal rotational barriers of different molecules. The calculated G3 and G3CEP barriers were accurate with respect to those obtained experimentally, typically showing deviations of <0.50 kcal mol⁻¹.

- 2198 **Mechanistic insights for β -cyclodextrin catalyzed phosphodiester hydrolysis** ,Mahboobeh Rahimian, Sachin D. Yeole, Shridhar P. Gejji [University of Pune]

Hydrolysis of phosphodiester bond in different substrates containing alkyl or aryl substituents, in the presence of β -cyclodextrin (β -CD) as a catalyst, has been investigated employing the density functional theory.

- 2197 **Theoretical study of oxidation of monovacancies in hexagonal boron nitride (h-BN) sheet by oxygen molecules** ,Jing-wen Feng, Jing-xiang Zhao [Harbin Normal University]

By performing density functional theory (DFT) calculations, we study the oxidation of monovacancies in hexagonal boron nitride (h-BN) sheet by oxygen molecules. In particular, the changes in structural, electronic, and magnetic properties of defective h-BN sheet are mainly addressed.

- 2196 **C α torsion angles as a flexible criterion to extract secrets from a molecular dynamics simulation** ,Fredrick Robin Devadoss Victor Paul Raj, Thomas E. Exner [Eberhard Karls University Tübingen]

Given the increasing complexity of simulated molecular systems, and the fact that simulation times have now reached milliseconds to seconds, immense amounts of data (in the gigabyte to terabyte range) are produced in current molecular dynamics simulations.

- 2195 **Electronic polarization stabilizes tertiary structure prediction of HP-36** ,Li L. Duan, Tong Zhu, Qing G. Zhang, Bo Tang [Shandong Normal University], John Z. H. Zhang

See Applications / Protein Folding.

- 2193 **Empty versus filled polyhedra: 11 vertex bare germanium clusters** ,Matei-Maria Uță, Robert Bruce King [University of Georgia]

The structures and energetics of centered 10-vertex Ge@Ge₁₀ z (z = -4, -2, 0, +2, +4) clusters have been investigated by density functional theory (DFT) for comparison with the previously studied isomeric empty 11-vertex Ge₁₁ z clusters.

- 2192 **Mutations in herpes simplex virus gD protein affect receptor binding by different molecular mechanisms** ,Joachim D. Stump, Heinrich Sticht [Friedrich-Alexander-Universität Erlangen-Nürnberg]

See Applications / Ligand Binding.

- 2190 **Calculation of the two-dimensional non-separable partition function for two molecular systems** ,Luis Simón-Carballido, Antonio Fernández-Ramos [Universidade de Santiago de Compostel]

We present the application of an accurate quantum treatment, called two-dimensional non-separable (2D-NS), to the calculation of internal rotation partition functions of molecules with two rotors.

- 2189 **Implementing electrostatic polarization cannot fill the gap between experimental and theoretical measurements for the ultrafast fluorescence decay of myoglobin** ,Bingbing Lin, Ya Gao, Yongxiu Li, John Z. H. Zhang, Ye Mei [East China Normal University]

Over the past few years, time-dependent ultrafast fluorescence spectroscopy method has been applied to the study of protein dynamics. However, observations from these experiments are in a controversy with other experimental studies.

- 2188 **Theoretical insight on novel donor-acceptor exTTF-based dyes for dye-sensitized solar cells** ,Joaquín Calbo, Pedro M. Viruela, Enrique Ortí [Universidad de Valencia]

A thorough density functional theory study is performed for the three carboxyl-based derivatives of the exTTF-TCF chromophore, where the π -extended tetrathiafulvalene (exTTF) electron-donor is linked to the tricyanofuran (TCF) electron-acceptor through an ethylene bridge, as dyes for dye-sensitized solar cells.

- 2187 **On the regioselectivity of the mononuclear copper-catalyzed cycloaddition of azide and alkynes (CuAAC). A quantum chemical topological study** ,Saturnino Calvo-Losada, María Soledad Pino, José Joaquín Quirante [Universidad de Málaga]

New density functional theory (DFT) calculations show that the nature of the mechanism for the classical copper-catalyzed cycloaddition of azide to terminal alkynes—widely known as the CuAAC reaction—also depends on the ligands attached to Cu(I).

- 2185 **Roles of electrostatic interaction and dispersion in $\text{CH}\cdots\text{CH}$, $\text{CH}\cdots\pi$, and $\pi\cdots\pi$ ethylene dimmers** ,Ye Cao, Ming Wah Wong [National University of Singapore]

Ab initio molecular orbital calculations were performed up to the CCSD(T)/CBS level to investigate the roles of the electrostatic interaction and dispersion in three basic types of intermolecular interaction, namely $\text{CH}\cdots\text{CH}$, $\text{CH}\cdots\pi$, and $\pi\cdots\pi$ interactions, in D2d, C2v, and Ci ethylene dimers, respectively.

- 2184 **Theoretical and experimental investigation of stability and spectra of doped Ag:ZnSe nanocrystals** ,Shuhong Xu, Chunlei Wang, Zhuyuan Wang, Yiping Cui [Southeast University]

In experiment, doped Ag:ZnSe nanocrystals (NCs) had better stability than that of ZnSe nanocrystals under ambient atmospheres in the presence of air and light illumination. However, it is difficult to explain the mechanism of better stability of Ag:ZnSe nanocrystals from the experiment perspective for doped nanocrystals are more unstable than corresponding pure nanocrystals in general.

- 2183 **A quantum chemistry study on thermochemical properties of high energy-density endothermic hydrocarbon fuel JP-10** ,Xiao-Mei Qin, Hu-Jun Xie, Lei Yue, Xiao-Xing Lu, Wen-Jun Fang[Zhejiang University]

The density functional theory (DFT) calculations at the M06-2X/6-31++G(d,p) level have been performed to explore the molecular structure, electronic structure, C-H bond dissociation enthalpy, and reaction enthalpies for five isodesmic reactions of a high energy-density endothermic hydrocarbon fuel JP-10.

- 2182 **A quantum chemistry study of natural gas hydrates** ,Mert Atilhan, Nezih Pala, Santiago Aparicio[University of Burgos]

The structure and properties of natural gas hydrates containing hydrocarbons, CO₂, and N₂ molecules were studied by using computational quantum chemistry methods via the density functional theory approach.

- 2180 **Mechanical, electronic, and optical properties of Bi₂S₃ and Bi₂Se₃ compounds: first principle investigations** ,Husnu Koc [Siirt University], Hacı Ozisik, Engin Deligöz, Amirullah M. Mamedov, Ekmel Ozbay

The structural, mechanical, electronic, and optical properties of orthorhombic Bi₂S₃ and Bi₂Se₃ compounds have been investigated by means of first principles calculations. The calculated lattice parameters and internal coordinates are in very good agreement with the experimental findings.

- 2179 **Mechanism of OH-initiated atmospheric oxidation of E/Z-CF₃CF = CF₃CF₃: a quantum mechanical study** ,Li-ling Ai, Jing-yao Liu[Jilin University]

A detailed theoretical investigation was performed on the mechanisms for the reactions of E/Z-CF₃CF = CF₃CF₃ with OH radicals by means of density functional theory (DFT). The geometries and frequencies of all the stationary points and the minimum energy path (MEP) are calculated at the M06-2X/aug-cc-pVDZ level.

- 2178 **Discovery of new druggable sites in the anti-cholesterol target HMG-CoA reductase by computational alanine scanning mutagenesis** ,D. S. Gesto, N. M. F. S. A. Cerqueira, M. J. Ramos, P. A. Fernandes [University of Porto]

See Applications / Enzyme Catalysis.

- 2176 **Determination of the shape and curvature of nonplanar lipid bilayers that are bent in a single plane in molecular dynamics simulations** ,S. O. Yesylevskyy [Institute of Physics of the National Academy of Sciences of Ukraine], S. Kraszewski, C. Ramseyer

See Applications / membrane proteins and lipid- peptide Interaction.

- 2173 **Mechanistic aspects of the lycopodine Michael-Claisen domino cyclization** ,Wilhelm A. Eger, Ernst Anders, Craig M. Williams [University of Queensland]

The Michael-Claisen domino (MCD) cyclization used in the lycopodine synthesis by Stork, was evaluated mechanistically using DFT calculations. Calculations suggest that a dianion is not formed, which conforms to classical dianion formation normally requiring strong kinetic bases.

- 2172 **Multipolar electrostatics based on the Kriging machine learning method: an application to serine** ,Yongna Yuan, Matthew J L Mills, Paul LA Popelier [University of Manchester]

A multipolar, polarizable electrostatic method for future use in a novel force field is described. Quantum Chemical Topology (QCT) is used to partition the electron density of a chemical system into atoms, then the machine learning method Kriging is used to build models that relate the multipole moments of the atoms to the positions of their surrounding nuclei.

- 2170 **Sumanene and its adsorption properties towards CO, CO₂ and NH₃ molecules** ,Stevan Armaković [University of Novi Sad], Sanja J. Armaković, Jovan P. Šetrajčić, Stevo K. Jaćimovski, Vladimir Holodkov

Density functional theory calculations were used in the theoretical investigation of the adsorption properties of sumanene towards molecules considered as common air pollutants: CO, CO₂ and NH₃. The insignificant perturbation of sumanene after adsorption and the adsorption energies obtained indicate a physisorption mechanism.

- 2167 **A combined experimental and computational study of the esterification reaction of glycerol with acetic acid** ,Gabriel Alejandro Bedogni, Cristina Liliana Padró, Nora Beatriz Okulik [Universidad Nacional del Chaco Austral]

This work describes theoretical and experimental studies on glycerol esterification to obtain acetins focusing on the obtained isomers. The reaction of glycerol with acetic acid was carried out on Amberlyst 36 wet.

- 2166 **Definition of the binding mode of phosphoinositide 3-kinase α -selective inhibitor A-66S through molecular dynamics simulation** ,Xiaoli Bian, Wangqing Dong, Yang Zhao, Rui Sun, Wanjun Kong, Yiping Li [Xi'an Jiaotong University]

See Applications / Ligand Binding.

- 2164 **Two new atom centered fragment descriptors and scoring function enhance classification of antibacterial activity** ,Durga Datta Kandel, Chandan Raychaudhury, Debnath Pal [Indian Institute of Science, Bangalore]

Classification of pharmacologic activity of a chemical compound is an essential step in any drug discovery process. We develop two new atom-centered fragment descriptors (vertex indices) - one based solely on topological considerations without discriminating atom or bond types, and another based on topological and electronic features.

- 2163 **Switching the conductance of a molecular junction using a proton transfer reaction** ,Chriszandro Hofmeister, Rainer Härtle, Óscar Rubio-Pons, Pedro B. Coto, Andrzej L. Sobolewski, Michael Thoss [Friedrich-Alexander-Universität Erlangen-Nürnberg]

A novel mechanism for switching a molecular junction based on a proton transfer reaction triggered by an external electrostatic field is proposed. As a specific example to demonstrate the feasibility of the mechanism, the tautomers [2,5-(4-hydroxypyridine)] and {2,5-[4(1H)-pyridone]} are considered.

- 2161 **Acidity in DMSO from the embedded cluster integral equation quantum solvation model** ,Jochen Heil, Daniel Tomazic, Simon Egbers, Stefan M. Kast [Technische Universität Dortmund]

The embedded cluster reference interaction site model (EC-RISM) is applied to the prediction of acidity constants of organic molecules in dimethyl sulfoxide (DMSO) solution. EC-RISM is based on a self-consistent treatment of the solute's electronic structure and the solvent's structure by coupling quantum-chemical calculations with three-dimensional (3D) RISM integral equation theory.

- 2160 **ReaxFF molecular dynamics simulations of CO collisions on an O-preadsorbed silica surface** ,Pablo Gamallo, Hèctor Prats, Ramón Sayós [University of Barcelona]

A quasiclassical trajectory dynamics study was performed for carbon monoxide collisions over an oxygen preadsorbed β -cristobalite (001) surface. A reactive molecular force field (ReaxFF) was used to model the potential energy surface.

- 2158 **Theoretical investigation on the crystal structures and electron transport properties of several nitrogen-rich pentacene derivatives** ,Caibin Zhao, Hongguang Ge, Shiwei Yin, Wenliang Wang [Shaanxi Normal University]

In the current work, the electron transport properties of four novel nitrogen-rich pentacene derivatives (PBD1, PBD2, PBD3, and PBD4) with two cyano groups as potential n-channel OFET materials have been investigated at the molecular and crystal levels by means of density functional theory (DFT) calculations coupled with the prediction of crystal structures and the incoherent charge-hopping model.

- 2155 **Theoretical investigation on the structure and performance of N, N'-azobis-polynitrodiazoles** ,Mei Jing, Huarong Li, Jun Wang [China Academy of Engineering Physics], Yuanjie Shu, Xiaoyu Zhang, Qing Ma, Yigang Huang

Six novel high energy density compounds of N, N'-azobis-polynitrodiazoles were designed. Their optimized geometric and electronic structures, band gaps, and heats of formation were explored at B3LYP/aug-cc-pVDZ level of density functional theory (DFT).

- 2148 **Computational investigations into the substituent effects of -N3, -NF2, -NO2, and -NH2 on the structure, sensitivity and detonation properties of N, N'-azobis(1, 2, 4-triazole)** ,Junqing Yang, Hua Yan, Guixiang Wang, Xueli Zhang, Tianyi Wang, Xuedong Gong [Nanjing University of Science and Technology]

A series of derivatives of N, N'-azobis(1, 2, 4-triazole) substituted by -N3, -NO2, -NF2, and -NH2 groups was studied using the density functional theory method.

- 2123 **Recognition of 2',5'-linked oligoadenylates by human ribonuclease L: molecular dynamics study**, Kamil Maláč, Ivan Barvík [Charles University]

See Applications / Enzyme Catalysis.

- 2118 **Novel hydrazine derivatives as selective DPP-IV inhibitors: findings from virtual screening and validation through molecular dynamics simulations** ,Omprakash Tanwar, Girdhar Singh Deora, Lalima Tanwar, Gautam Kumar, Sridhara Janardhan, Md. Mumtaz Alam, Md. Shaquiquzzaman, Mymoona Akhter [Bioinformatics Infrastructure Facility (BIF)]

See Applications / Ligand Binding.

- 2103 **Full kinetics investigation of the formation reaction of phosphonate esters in the gas-phase: a theoretical study** ,Mohammad Amin Kazemian, Sayyed Mostafa Habibi-Khorassani [University of Sistan and Baluchestan], Malek Taher Maghsoodlu, Ali Ebrahimi

In the present work, the proposed multiple-mechanisms have been investigated theoretically for the reaction between triphenyl phosphite and dimethyl acetylenedicarboxylate in the presence of N-H acid such as aniline for generation of phosphonate esters using ab initio molecular orbital theory in gas phase.

- 2100 **Theoretical study on absorption and emission spectra of adenine analogues** ,Hongxia Liu, Qixia Song, Yan Yang, Yan Li, Haijun Wang [Jiangnan University]

Fluorescent nucleoside analogues have attracted much attention in studying the structure and dynamics of nucleic acids in recent years. In the present work, we use theoretical calculations to investigate the structural and optical properties of four adenine analogues (termed as A1, A2, A3, and A4), and also consider the effects of aqueous solution and base pairing.

- 2098 **Molecular interaction of PCB180 to human serum albumin: insights from spectroscopic and molecular modelling studies** ,Senbiao Fang, Huanhuan Li, Tao Liu, Hongxia Xuan, Xin Li, Chunyan Zhao [LanzhouUniversity]

See Applications / Ligand Binding.

4. ADDRESSES OF PRINCIPAL AUTHORS

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About 125 Papers from more than 30 Journals are cited.

1 APPLICATIONS (74) Page 2

1.1 Small Molecules (12)

General and Model Systems	Page 2	Med. Chem. And Drug	Page 2

1.2 Biopolymers (62)

Bioinformatics and Cheminformatics	Page 6	Ligand Binding	Page 13
Protein Secondary Structure	Page 7	Enzyme Catalysis	Page 15
Comparitive or Homology Modeling	Page 8	Protein-Protein Interactions	Page 18
Protein Conformational Analysis	Page 8	Membrane Proteins	Page 19
Protein Structure Analysis	Page 10	Protein Folding	Page 21
Protein Dynamics	Page 11	Nucleic Acids	Page 22
Free Energy Calculations	Page 13		

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (27) Page 23

QSAR	Page 23	Free Energy Perturbation	Page 26
Potentials and Parameters	Page 25	QM & QM/MM Modeling	Page 27
Molecular Dynamics	Page 25	Ligand Docking	Page 29

3 JOURNAL REVIEWS (5) Page 31

Journal of Molecular Graphics and Modeling, 50, May, 2014.
 Journal of Computational Chemistry, 35 (12), May, 2014.
 Journal of Computational Chemistry, 35 (13), May, 2014.
 Journal of Computational Chemistry, 35 (14), May, 2014.
 Journal of Molecular Modeling, 20 (5), May, 2014.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 39

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1. APPLICATIONS

1.1. Small Molecules

General And Model Systems

Quantitative Predictions of the Interfacial Tensions of Liquid-Liquid Interfaces through Atomistic and Coarse Grained Models

Jean-Claude Neyt, Aurélie Wender, Véronique Lachet, Aziz Ghoufi, Patrice Malfreyt [Institut de Chimie de Clermont-Ferrand]

J. Chem. Theor. and Comp., **10**, 1887–1899, 2014.

We report molecular simulations of oil–water liquid–liquid interfaces by using atomistic and coarse grained (CG) MARTINI force fields. We also apply the electronic continuum (EC) model to the MARTINI force field for the calculation of the interfacial tension of oil/water-salt systems. In a first step, we propose to calculate the interfacial tensions using thermodynamic and mechanical definitions of hydrocarbon–water interfacial systems modified by the addition of salts and alcohol. We also establish here the order of magnitude of the long-range corrections to the interfacial tension in fluid–fluid interfaces.

Medicinal Chemistry and Drug Design

Role of ELA region in auto-activation of mutant KIT receptor: a molecular dynamics simulation insight

Rituraj Purohit [Vellore Institute of Technology University]

J. Biomol. Stru. and Dyn., **32**, 1033-1046, 2014.

KIT receptor is the prime target in gastrointestinal stromal tumor (GISTs) therapy. Second generation inhibitor, Sunitinib, binds to an inactivated conformation of KIT receptor and stabilizes it in order to prevent tumor formation. Here, we investigated the dynamic behavior of wild type and mutant D816H KIT receptor, and emphasized the extended A-loop (EAL) region (805–850) by conducting molecular dynamics simulation (~100 ns). We analyzed different properties such as root mean square cutoff or deviation, root mean square fluctuation, radius of gyration, solvent-accessible surface area, hydrogen bonding network analysis, and essential dynamics.



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Medicinal Chemistry and Drug Design (Cont'd)

NMR-based structure of anticancer drug mitoxantrone stacked with terminal base pair of DNA hexamer sequence d-(ATCGAT)₂

Shilpa Dogra, Pamita Awasthi [National Institute of Technology Hamirpur], Sweta Tripathi, T.P. Pradeep, Maya S. Nair, Ritu Barthwal

J. Biomol. Stru. and Dyn., 32, 1164-1183, 2014.

Mitoxantrone is a promising antitumor drug having considerably reduced cardiotoxicity as compared to anthracyclines. Its binding to deoxyhexanucleotides sequence d-(ATCGAT)₂ has been studied by proton and phosphorous-31 nuclear magnetic resonance spectroscopy. The stoichiometry reveals that 1:1 and 2:1 mitoxantrone-d(ATCGAT)₂ complexes are formed in solution. Significant upfield shifts in 6H/7H, 2H/3H, 11NH, and 12NH protons (~.5 ppm) of mitoxantrone and T6NH imino protons (~.3 ppm) are observed. The phosphorous resonances do not shift significantly indicating that the base pairs do not open at any nucleotide step along the sequence of hexamer.

Validation of potential inhibitors for SrtA against *Bacillus anthracis* by combined approach of ligand-based and molecular dynamics simulation

Chandrabose Selvaraj, Sanjeev Kumar Singh [Alagappa University]

J. Biomol. Stru. and Dyn., 32, 1333-1349, 2014.

The development of SrtA inhibitors targeting the biothreat organism namely *Bacillus anthracis* was achieved by the combined approach of pharmacophore modeling, binding interactions, electron transferring capacity, ADME, and Molecular dynamics studies. In this study, experimentally reported Ba-SrtA inhibitors (pyridazinone and pyrazolethione derivatives) were considered for the development of enhanced pharmacophoric model. The obtained AAAHR hypothesis was a pure theoretical concept that accounts for common molecular interaction network present in experimentally active pyridazinone and pyrazolethione derivatives.

Combined structure- and ligand-based pharmacophore modeling and molecular dynamics simulation studies to identify selective inhibitors of MMP-8

Sukesh Kalva, D. Vinod, Lilly M. Saleena [SRM University]

J. Mol.Mod., 20, 2191, 2014.

Matrix metalloproteinase-8 (MMP-8) is the key mediator in initiating type I collagen degradation and is associated with rheumatoid arthritis. In the present study, a pharmacophore hypothesis was developed based on selective non zinc binding inhibitors of MMP-8. This study proposes a combined structure- and ligand-based pharmacophore model that is suitable for retrieving the novel inhibitors of MMP-8. The pharmacophore hypothesis AADRH was used as query for retrieving potential compounds from the Zinc database and hits were selected based on the catalytic selective amino acid residues of Arg 222, and Tyr 227.

Medicinal Chemistry and Drug Design (Cont'd)

Structure- and ligand-based drug design of novel p38- α MAPK inhibitors in the fight against the Alzheimer's disease

Flávio Roberto Pinsetta, Carlton Anthony Taft[Centro Brasileiro de Pesquisas Físicas], Carlos Henrique Tomich de Paula da Silva

J. Biomol. Stru. and Dyn., 32, 1047-1063, 2014.

Alzheimer's disease (AD) is characterized microscopically by the presence of amyloid plaques, which are accumulations of beta-amyloid protein inter-neurons, and neurofibrillary tangles formed predominantly by highly phosphorylated forms of the microtubule-associated protein, tau, which form tangled masses that consume neuronal cell body, possibly leading to neuronal dysfunction and ultimately death. p38 α mitogen-activated protein kinase (MAPK) has been implicated in both events associated with AD, tau phosphorylation and inflammation. p38 α MAPK pathway is activated by a dual phosphorylation at Thr180 and Tyr182 residues. Here, we used different approaches of structure- and ligand-based drug design and medicinal chemistry strategies based on a selected p38 α MAPK structure deposited in the Protein Data Bank in complex with inhibitor, as well as others reported in literature.

SVM Classification and CoMSIA Modeling of UGT1A6 Interacting Molecules

Leo Ghemtio, Anne Soikkeli, Marjo Yliperttula, Jouni Hirvonen, Moshe Finel, Henri Xhaard [University of Helsinki]

J.Chem. Infor. and Mod. 54, 1011–1026, 2014.

The human UDP-glucuronosyltransferase 1A6 (UGT1A6) plays important roles in elimination of many xenobiotics, including drugs. We have experimentally assessed inhibitory properties of 46 compounds toward UGT1A6 catalyzing the glucuronidation of 1-naphthol and built models for predicting compounds interactions with the enzyme. The tested compounds were divided into a training set ($n = 31$; evaluated by 10-fold cross-validation) and an external test set ($n = 15$), both of which yielded similar accuracies (80–81%) and Matthews correlation coefficients (0.61–0.63) when classified using support vector machines.

AlzPlatform: An Alzheimer's Disease Domain-Specific Chemogenomics Knowledgebase for Polypharmacology and Target Identification Research

Haibin Liu, Lirong Wang, Mingliang Lv, Rongrong Pei, Peibo Li, Zhong Pei, Yonggang Wang, Weiwei Su, Xiang-Qun Xie [University of Pittsburgh]

J.Chem. Infor. and Mod. 54, 1050–1060, 2014.

Alzheimer's disease (AD) is one of the most complicated progressive neurodegeneration diseases that involve many genes, proteins, and their complex interactions. No effective medicines or treatments are available yet to stop or reverse the progression of the disease due to its polygenic nature. To facilitate discovery of new AD drugs and better understand the AD neurosignaling pathways involved, we have constructed an Alzheimer's disease domain-specific chemogenomics knowledgebase, AlzPlatform (www.cbiligand.org/AD/) with cloud computing and sourcing functions. AlzPlatform is implemented with powerful computational algorithms, including our established TargetHunter, HTDocking, and BBB Predictor for target identification and polypharmacology analysis for AD research.

Medicinal Chemistry and Drug Design (Cont'd)

Novel Mycosin Protease MycP1 Inhibitors Identified by Virtual Screening and 4D Fingerprints

Adel Hamza, Jonathan M. Wagner, Timothy J. Evans, Mykhaylo S. Frasinuk, Stefan Kwiatkowski, Chang-Guo Zhan, David S. Watt, Konstantin V. Korotkov [University of Kentucky]

J.Chem. Infor. and Mod. **54**, 1166–1173, 2014.

The rise of drug-resistant *Mycobacterium tuberculosis* lends urgency to the need for new drugs for the treatment of tuberculosis (TB). The identification of a serine protease, mycosin protease-1 (MycP1), as the crucial agent in hydrolyzing the virulence factor, ESX-secretion-associated protein B (EspB), potentially opens the door to new tuberculosis treatment options. Using the crystal structure of mycobacterial MycP1 in the apo form, we performed an iterative ligand- and structure-based virtual screening (VS) strategy to identify novel, nonpeptide, small-molecule inhibitors against MycP1 protease.

De Novo Design of Multitarget Ligands with an Iterative Fragment-Growing Strategy

Erchang Shang, Yaxia Yuan, Xinyi Chen, Ying Liu, Jianfeng Pei, Luhua Lai [Peking University]

J.Chem. Infor. and Mod. **54**, 1235–1241, 2014.

In this paper, we report the first de novomultitarget ligand design method, with an iterative fragment-growing strategy. Using this method, dual-target inhibitors for COX-2 and LTA4H were designed, with the most potent one inhibiting PGE2 and LTB4 production in the human whole blood assay with IC50 values of 7.0 and 7.1 μ M, respectively. Our strategy is generally applicable in rational and efficient multitarget drug design, especially for the design of highly integrated inhibitors for proteins with dissimilar binding pockets.

Identification of Novel Potential Antibiotics against Staphylococcus Using Structure-Based Drug Screening Targeting Dihydrofolate Reductase

Maiko Kobayashi, Tomohiro Kinjo, Yuji Koseki, Christina R. Bourne, William W. Barrow, Shunsuke Aoki [Kyushu Institute of Technology,]

J.Chem. Infor. and Mod. **54**, 1242–1253, 2014.

The emergence of multidrug-resistant *Staphylococcus aureus* (S. aureus) makes the treatment of infectious diseases in hospitals more difficult and increases the mortality of the patients. In this study, we attempted to identify novel potent antibiotic candidate compounds against S. aureus dihydrofolate reductase (saDHFR). We performed three-step in silico structure-based drug screening (SBDS) based on the crystal structure of saDHFR using a 154,118 chemical compound library. We subsequently evaluated whether candidate chemical compounds exhibited inhibitory effects on the growth of the model bacterium: *Staphylococcus epidermidis* (S. epidermidis).

Mapping disease-related missense mutations in the immunoglobulin-like fold domain of lamin A/C reveals novel genotype–phenotype associations for laminopathies

Juergen Scharner, Hui-Chun Lu, Franca Fraternali, Juliet A. Ellis, Peter S. Zammit [King's College London]

Proteins: Stru. Fun. & Bioinf., **82**, 904–915, 2014.

Mutations in A-type nuclear lamins cause laminopathies. However, genotype–phenotype correlations using the 340 missense mutations within the LMNA gene are unclear: partially due to the limited availability of three-dimensional structure. The immunoglobulin (Ig)-like fold domain has been solved, and using bioinformatics tools (including Polyphen-2, Fold X, Parameter Optimized Surfaces, and PocketPicker) we characterized 56 missense mutations for position, surface exposure, change in charge and effect on Ig-like fold stability.

1.2. Biopolymers

Bioinformatics and Cheminformatics

ST-analyzer: A web-based user interface for simulation trajectory analysis

Jong Cheol Jeong, Sunhwan Jo, Emilia L. Wu, Yifei Qi, Viviana Monje-Galvan, Min Sun Yeom, Lev Gorenstein, Feng Chen, Jeffery B. Klauda, Wonpil Im [The University of Kansas]

J. Comp. Chem., **35**, 957–963, 2014.

Molecular dynamics (MD) simulation has become one of the key tools to obtain deeper insights into biological systems using various levels of descriptions such as all-atom, united-atom, and coarse-grained models. Recent advances in computing resources and MD programs have significantly accelerated the simulation time and thus increased the amount of trajectory data. Although many laboratories routinely perform MD simulations, analyzing MD trajectories is still time consuming and often a difficult task. ST-analyzer, <http://im.bioinformatics.ku.edu/st-analyzer>, is a standalone graphical user interface (GUI) toolset to perform various trajectory analyses.

Midpoint cell method for hybrid (MPI+OpenMP) parallelization of molecular dynamics simulations

Jaewoon Jung, Takaharu Mori, Yuji Sugita [RIKEN Theoretical Molecular Science Laboratory]

J. Comp. Chem., **35**, 1064–1072, 2014.

We have developed a new hybrid (MPI+OpenMP) parallelization scheme for molecular dynamics (MD) simulations by combining a cell-wise version of the midpoint method with pair-wise Verlet lists. In this scheme, which we call the midpoint cell method, simulation space is divided into subdomains, each of which is assigned to a MPI processor. Each subdomain is further divided into small cells. The interaction between two particles existing in different cells is computed in the subdomain containing the midpoint cell of the two cells where the particles reside.

ALMOST: An all atom molecular simulation toolkit for protein structure determination

Biao Fu, Aleksandr B. Sahakyan, Carlo Camilloni, Gian Gaetano Tartaglia, Emanuele Paci, Amedeo Caflisch, Michele Vendruscolo, Andrea Cavalli [University of Cambridge]

J. Comp. Chem., **35**, 1101–1105, 2014.

Almost (all atom molecular simulation toolkit) is an open source computational package for structure determination and analysis of complex molecular systems including proteins, and nucleic acids. **Almost** has been designed with two primary goals: to provide tools for molecular structure determination using various types of experimental measurements as conformational restraints, and to provide methods for the analysis and assessment of structural and dynamical properties of complex molecular systems.

Bioinformatics and Cheminformatics (Cont'd)

Chemical Structure Elucidation from ^{13}C NMR Chemical Shifts: Efficient Data Processing Using Bipartite Matching and Maximal Clique Algorithms

Shungo Koichi [Nanzan University], Masaki Arisaka, Hiroyuki Koshino, Atsushi Aoki, Satoru Iwata, Takeaki Uno, Hiroko Satoh

J.Chem. Infor. and Mod. **54**, 1027–1035, 2014.

Computer-assisted chemical structure elucidation has been intensively studied since the first use of computers in chemistry in the 1960s. Most of the existing elucidators use a structure–spectrum database to obtain clues about the correct structure. Such a structure–spectrum database is expected to grow on a daily basis. Hence, the necessity to develop an efficient structure elucidation system that can adapt to the growth of a database has been also growing. Therefore, we have developed a new elucidator using practically efficient graph algorithms, including the convex bipartite matching, weighted bipartite matching, and Bron–Kerbosch maximal clique algorithms.

SAMPL4 & DOCK3.7: lessons for automated docking procedures

Ryan G. Coleman [University of California], Teague Sterling

J. Comp. Aided. Mol. Design, **28**, 201–209, 2014.

The SAMPL4 challenges were used to test current automated methods for solvation energy, virtual screening, pose and affinity prediction of the molecular docking pipeline DOCK 3.7. Additionally, first-order models of binding affinity were proposed as milestones for any method predicting binding affinity. Several important discoveries about the molecular docking software were made during the challenge. Overall, lessons from SAMPL4 suggest many changes to molecular docking tools, not just DOCK 3.7, that could improve the state of the art. Future difficulties and projects will be discussed.

Protein Secondary Structure

Structure prediction of GPCRs using piecewise homologs and application to the human CCR5 chemokine receptor: validation through agonist and antagonist docking

Karthik Arumugam [Laboratoire de Rétrovirologie], Serge Crouzy, Andy Chevigne, Carole Seguin-Devaux, Jean-Claude Schmit

J. Biomol. Stru. and Dyn., **32**, 1274–1289, 2014.

This article describes the construction and validation of a three-dimensional model of the human CC chemokine receptor 5 (CCR5) receptor using multiple homology modeling. A new methodology is presented where we built each secondary structural model of the protein separately from distantly related homologs of known structure. The reliability of our approach for G-protein coupled receptors was assessed through the building of the human C-X-C chemokine receptor type 4 (CXCR4) receptor of known crystal structure. The models are refined using molecular dynamics simulations and energy minimizations using CHARMM, a classical force field for proteins.

Protein Secondary Structure (Cont'd)

Molecular Dynamics Investigations of the α -Helix to β -Barrel Conformational Transformation in the RfaH Transcription Factor

Jeevan B. GC, Yuba R. Bhandari, Bernard S. Gerstman, Prem P. Chapagain [Florida International University]

J. Phys. Chem. B., **118**, 5101–5108, 2014.

We used replica exchange molecular dynamics simulations with implicit solvent to investigate the α -helix to β -structure transformation of RfaH-CTD, followed by structural relaxation with detailed all atom simulations for the best replica. The importance of interfacial interactions between the two domains of RfaH is highlighted by the compromised structural integrity of the helical form of the CTD in the absence NTD. Calculations of free-energy landscape and transfer entropy elucidate the details of the RfaH-CTD transformation process.

Comparative or Homology Modeling

Antiapoptotic Bcl-2 homolog CED-9 in *Caenorhabditis elegans*: Dynamics of BH3 and CED-4 binding regions and comparison with mammalian antiapoptotic Bcl-2 proteins

Vivek Modi , Ramasubbu Sankararamakrishnan [Indian Institute of Technology Kanpur,]

Proteins: Stru. Fun. & Bioinf., **82**, 1035–1047, 2014.

We have performed molecular dynamics simulations of CED-9 in two forms and compared the results with those of mammalian counterparts Bcl-X_L, Bcl-w, and Bcl-2. Our studies demonstrate that the region forming the hydrophobic cleft is more flexible compared with the CED-4-binding region, and this is generally true for all antiapoptotic Bcl-2 proteins studied. CED-9 is the most stable protein during simulations and its hydrophobic pocket is relatively rigid explaining the absence of functional redundancy in CED-9.

Protein Conformational Analysis

Molecular dynamics investigation on the poor sensitivity of A171T mutant NEDD8-activating enzyme (NAE) for MLN4924

Sharad Verma, Amit Singh , Abha Mishra[Banaras Hindu University]

J. Biomol. Stru. and Dyn., **32**, 1064-1073,2014.

MLN4924 is an adenosine sulfamate analog that generates the inhibitory NEDD8-MLN4924 covalent complex. A single nucleotide transition that changes alanine 171 to threonine (A171T) of the NAE subunit UBA3 reduces the enzyme's sensitivity for MLN4924. Our molecular dynamics simulation study revealed that A171T transition brought remarkable conformational changes in enzyme structure (open ATP binding pocket), which reduced the interaction between MLN4924 and ATP binding pocket while wild form completely covered the MLN4924.

Protein Conformational Analysis (Cont'd)

Structural insight into a novel human CCR5-V130I variant associated with resistance to HIV-1 infection

Nejla Stambouli [Immunology and Human Pathology, Tunis], Ning-Ning Wei, Asma Jlizi, Samah Aissa, Rim Abdelmalek, Baderredine Kilani, Amine Slim, Ben Aissa Hanen Tiouiri, Mahdi Dridi, Adel Hamza & Amel Ben Ammar Elgaied

J. Biomol. Stru. and Dyn., 32, 1202-1210, 2014.

We report the identification of a novel CC chemokine receptor 5 (CCR5) variant that seems associated with resistance to HIV-1 infection. The V130I mutation of the CCR5 receptor is located in the intracellular loop ICL2 known as DRY box and described in the literature as a nonsynonymous mutation present in nonhuman primates group. Extensive molecular modeling and dynamics simulations were performed to elucidate the mechanism by which the V130I mutation may induce conformational change of the CCR5 folding protein and prevent the interaction with the β -arrestin protein.

Fosfomycin Induced Structural Change in Fosfomycin Resistance Kinases FomA: Molecular Dynamics and Molecular Docking Studies

Yun-Jian Wu, Qing-Chuan Zheng, Ji-Long Zhang, Wen-Ting Chu, Ying-Lu Cui, Yan Wang, Hong-Xing Zhang [Jilin University]

J. Mol.Mod., 20, 2236, 2014.

Fosfomycin resistance kinases FomA, one of the key enzymes responsible for bacterial resistances to fosfomycin, has gained much attention recently due to the raising public concern for multi-drug resistant bacteria. Using molecular docking followed by molecular dynamics simulations, our group illustrated the process of fosfomycin induced conformational change of FomA. The detailed roles of the catalytic residues (Lys18, His58 and Thr210) during the formation of the enzyme-substrate complex were shown in our research.

Screen3D: A Novel Fully Flexible High-Throughput Shape-Similarity Search Method

Adrián Kalászi, Dániel Szisz, Gábor Imre, Tímea Polgár [Graphisoft park]

J.Chem. Infor. and Mod. 54, 1036–1049, 2014.

3D shape- or volume-based virtual screening is a broadly used approach in drug discovery. In recent years a large number of publications have appeared in which these tools were compared not only to competitive methods but to docking studies as well. Studies often showed that the effectiveness of docking could be highly variable due to a large number of possible confounding factors, while ligand-based, shape-based approaches were more consistent.

Molecular Dynamics Study of the Phosphorylation Effect on the Conformational States of the C-Terminal Domain of RNA Polymerase II

Yasushige Yonezawa [Kinki University]

J. Phys. Chem. B., 118, 4471–4478, 2014.

The carboxyl-terminal domain (CTD) of RNA polymerase II in eukaryotes regulates mRNA processing processes by recruiting various regulation factors. A main function of the CTD relies on the heptad consensus sequence (YSPTSPS). The CTD dynamically changes its conformational state to recognize and bind different regulation factors. The dynamical conformation changes are caused by modifications, mainly phosphorylation and dephosphorylation, to the serine residues. In this study, we investigate the conformational states of the unit consensus CTD peptide with various phosphorylation patterns of the serine residues by extended ensemble simulations.

Protein Structure Analysis

The addition of 2,2,2-trifluoroethanol prevents the aggregation of guanidinium around protein and impairs its denaturation ability: A molecular dynamics simulation study

Qiang Shao[Shanghai Institute of Materia Medica]

Proteins: Stru. Fun. & Bioinf., **82**, 944–953, 2014.

The present molecular dynamics simulation study shows a novel test to investigate the combined effects of TFE and Gdm⁺ on protein structure in mixed guanidinium/TFE solution. The results indicate that the accumulation of TFE is more competitive than Gdm⁺ in either GdmSCN/TFE or GdmCl/TFE solution. The preceding accumulation of TFE around protein surface limits the approach of Gdm⁺ and water to protein. As a result, the hydrogen bonding between Gdm⁺ and water to protein is highly forbidden and the secondary structure stability of protein is strongly enhanced. In contrast, without the presence of TFE, the protein structure is largely denatured in similarly concentrated GdmSCN or GdmCl solution.

Structural Analysis of α -Fetoprotein (AFP)-like Peptides with Anti-Breast-Cancer Properties

Berhane Temelso, Katherine A. Alser, Arianne Gauthier, Amber Kay Palmer, George C. Shields [Bucknell University]

J. Phys. Chem. B., **118**, 4514–4526, 2014.

The abundance of α -fetoprotein (AFP), a natural protein produced by the fetal yolk sac during pregnancy, correlates with lower incidence of estrogen receptor positive (ER⁺) breast cancer. The pharmacophore region of AFP has been narrowed down to a four amino acid (AA) region in the third domain of the 591 AA peptide. Our computational study focuses on a 4-mer segment consisting of the amino acids threonine-proline-valine-asparagine (TPVN). We have run replica exchange molecular dynamics (REMD) simulations and used 120 configurational snapshots from the total trajectory as starting configurations for quantum chemical calculations.

An Investigation of G-Quadruplex Structural Polymorphism in the Human Telomere Using a Combined Approach of Hydrodynamic Bead Modeling and Molecular Dynamics Simulation

Huy T. Le, William L. Dean, Robert Buscaglia, Jonathan B. Chaires, John O. Trent [University of Louisville]

J. Phys. Chem. B., **118**, 5390–5405, 2014.

Guanine-rich oligonucleotides can adopt noncanonical tertiary structures known as G-quadruplexes, which can exist in different forms depending on experimental conditions. We have used molecular dynamics in conjunction with hydrodynamic bead modeling to study the structures of the human telomeric G-quadruplex-forming sequences at the atomic level. We demonstrated that molecular dynamics can reproduce experimental hydrodynamic measurements and thus can be a powerful tool in the structural study of existing G-quadruplex sequences or in the prediction of new G-quadruplex structures.

Protein Dynamics

Internal Nanosecond Dynamics in the Intrinsically Disordered Myelin Basic Protein

Andreas M. Stadler [Jülich Centre for Neutron Science JCNS and Institute for Complex Systems ICS], Laura Stingaciu, Aurel Radulescu, Olaf Holderer, Michael Monkenbusch, Ralf Biehl, Dieter Richter

J. Am. Chem. Soc., 2013, **136**, 6987–6994, 2014.

Intrinsically disordered proteins lack a well-defined folded structure and contain a high degree of structural freedom and conformational flexibility, which is expected to enhance binding to their physiological targets. In solution and in the lipid-free state, myelin basic protein belongs to that class of proteins. Using small-angle scattering, the protein was found to be structurally disordered similar to Gaussian chains. The combination of structural and hydrodynamic information revealed an intermediary compactness of the protein between globular proteins and random coil polymers.

Modeling stability and flexibility of α -Chymotrypsin in room temperature ionic liquids

Muhammad A.M. Latif, Bimo A. Tejo, Roghayeh Abedikargiban, Mohd B. Abdul Rahman & Nuno M. Micaêlo [Minho University]

J. Biomol. Stru. and Dyn., 32, 1263-1273, 2014.

We investigate the structure and dynamics of α -Chymotrypsin in five room temperature ionic liquids (RTILs) sharing a common cation, hydrated with different water percentages (w/w) (weight of water over protein). Results from molecular dynamics simulations are correlated with experimental evidences from studies on the activity of enzymes in RTILs. α -Chymotrypsin protein structure is closer to its native crystallographic structure in RTILs than in aqueous environment. We show that the structural properties of α -Chymotrypsin were affected by the water concentration assayed in a typical bell-shaped profile, which is also frequently reported for organic solvents.

A Cooperative Mechanism of Clotrimazoles in P450 Revealed by the Dissociation Picture of Clotrimazole from P450

Mian Wang, Marc Baaden, Jianyi Wang [Guangxi University], Zhiqun Liang

J. Chem. Infor. and Mod. **54**, 1218–1225, 2014.

The dissociation processes of clotrimazole (CLT) in several models are comparatively investigated by molecular dynamics simulations to explore the cooperative mechanism of clotrimazoles in P450. Our results suggest that when P450 only accommodates the active CLT (CLT1), CLT1 continually diffuses away from heme, and the partial BC loop (residues 73–88) and the extended FG loop (residues 173–186) first close and then open. When the enzyme binds to two CLT molecules, CLT1 basically keeps close to heme, and the partial BC loop and the extended FG loop move close to each other.

Mesoscopic Coarse-Grained Simulations of Lysozyme Adsorption

Gaobo Yu, Jie Liu, Jian Zhou [South China University of Technology]

J. Phys. Chem. B., **118**, 4451–4460, 2014.

Coarse-grained simulations are adopted to study the adsorption behavior of lysozyme on different (hydrophobic, neutral hydrophilic, zwitterionic, negatively charged, and positively charged) surfaces at the mesoscopic microsecond time scale (1.2 μ s). Simulation results indicate the following: (i) the conformation change of lysozyme on the hydrophobic surface is bigger than any other studied surfaces; (ii) the active sites of lysozyme are faced to the hydrophobic surface with a “top end-on” orientation, while they are exposed to the liquid phase on the hydrophilic surface with a “back-on” orientation;

Protein Dynamics (Cont'd)

Structure and Dynamics of a Fusion Peptide Helical Hairpin on the Membrane Surface: Comparison of Molecular Simulations and NMR

Allyn R. Brice , Themis Lazaridis [City College of New York]

J. Phys. Chem. B., **118**, 4461–4470, 2014.

The conserved N-terminal residues of the HA2 subunit of influenza hemagglutinin (fusion peptide) are essential for membrane fusion and viral entry. Recent NMR studies showed that the 23-residue fusion peptide forms a helical hairpin that undergoes rocking motion relative to the membrane surface on a nanosecond time scale. To compare with NMR and to obtain a detailed molecular picture of the peptide–membrane interaction, we performed molecular dynamics simulations of the fusion peptide in explicit dimyristoylphosphatidylcholine and with the IMM1 implicit membrane model.

Ion-Specific Induced Fluctuations and Free Energetics of Aqueous Protein Hydrophobic Interfaces: Toward Connecting to Specific-Ion Behaviors at Aqueous Liquid–Vapor Interfaces

Di Cui, Shuching Ou, Eric Peters, Sandeep Patel [University of Delaware]

J. Phys. Chem. B., **118**, 4490–4504, 2014.

We consider the anions chloride and iodide that have been shown previously by simulations as displaying specific-ion behaviors at aqueous liquid–vapor interfaces. We find that as in the case of a pure liquid–vapor interface, at the hydrophobic protein–water interface, the larger, less charge-dense iodide anion displays a marginal interfacial stability compared with that of the smaller, more charge-dense chloride anion. Furthermore, consistent with the results at aqueous liquid–vapor interfaces, we find that iodide induces larger fluctuations of the protein–water interface than chloride.

Conformational Adaptation in the E. coli Sigma 32 Protein in Response to Heat Shock

Abhijit Chakraborty, Srijata Mukherjee, Ruchira Chattopadhyay, Siddhartha Roy, and Saikat Chakrabarti [CSIR-Indian Institute of Chemical Biology]

J. Phys. Chem. B., **118**, 4793–4802, 2014.

In this study, we have modeled the E. coli σ 32 structure by homology modeling and conducted extensive molecular dynamics (MD) simulations at non-heat-shock (30 °C) and heat-shock (42 °C) temperatures. Substantial structural rearrangements at 42 °C were observed around the N-terminus (residues 11–60, which cover the DnaJ binding region) and the region spanning residues 190–210 (covering the DnaK binding site, residues 198–201). At 42 °C, a large amount of helix melting and structural destabilization was observed around residues 11–60, while regions 91–101 and 216–221 of σ 32 undergo conformational change, leading to formation of a lid-like structure over region 198-VLYL-201 resulting in reduced accessibility of the DnaK binding sites.

3D Structures and Redox Potentials of Cu²⁺–A β (1–16) Complexes at Different pH: A Computational Study

Jorge Alí-Torres, Andrea Mirats, Jean-Didier Maréchal, Luis Rodríguez-Santiago, Mariona Sodupe [Universitat Autònoma de Barcelona]

J. Phys. Chem. B., **118**, 4840–4850, 2014.

Oxidative stress induced by redox-active metal cations such as Cu²⁺ is a key event in the development of Alzheimer's disease. A detailed knowledge of the structure of Cu²⁺–A β complex is thus important to get a better understanding of this critical process. In the present study, we use a computational approach that combines homology modeling with quantum-mechanics-based methods to determine plausible 3D structures of Cu²⁺–A β (1–16) complexes that enclose the different metal coordination spheres proposed experimentally at different pH values.

Protein Dynamics (Cont'd)

Dissecting the Effects of Concentrated Carbohydrate Solutions on Protein Diffusion, Hydration, and Internal Dynamics

Enrico Spiga, Luciano A. Abriata, Francesco Piazza, Matteo Dal Peraro [École Polytechnique Fédérale de Lausanne (EPFL)]

J. Phys. Chem. B., **118**, 5310–5321, 2014.

We present herein a thorough description of the effects of high glucose concentrations on the diffusion, hydration and internal dynamics of ubiquitin, as predicted from extensive molecular dynamics simulations on several systems described at fully atomistic level. We observe that the protein acts as a seed that speeds up the natural propensity of glucose to cluster at high concentration; the sugar molecules thus aggregate around the protein trapping it inside a dynamic cage. This process extensively dehydrates the protein surface, restricts the motions of the remaining water molecules, and drags the large-scale, collective motions of protein atoms slowing down the rate of exploration of the conformational space despite only a slight dampening of fast, local dynamics.

Free Energy Calculations

Blind prediction of solvation free energies from the SAMPL4 challenge

David L. Mobley[University of California], Karisa L. Wymer, Nathan M. Lim, J. Peter Guthrie

J. Comp. Aided. Mol. Design, **28**, 135-150, 2014.

Here, we give an overview of the small molecule hydration portion of the SAMPL4 challenge, which focused on predicting hydration free energies for a series of 47 small molecules. These gas-to-water transfer free energies have in the past proven a valuable test of a variety of computational methods and force fields. Here, in contrast to some previous SAMPL challenges, we find a relatively wide range of methods perform quite well on this test set, with RMS errors in the 1.2 kcal/mol range for several of the best performing methods.

Ligand Binding/Docking

Unraveling the binding mechanism of asiatic acid with human serum albumin and its biological implications

Mahesh Gokara, Tirupathi Malavath, Suresh Kumar Kalangi, Pallu Reddana, Rajagopal Subramanyam[University of Hyderabad]

J. Biomol. Stru. and Dyn., **32**, 1290-1302, 2014.

Asiatic acid (AsA), a naturally occurring pentacyclic triterpenoid found in *Centella asiatica*, plays a major role in neuroprotection, anticancer, antioxidant, and hepatoprotective activities. Human serum albumin (HSA), a blood plasma protein, participates in the regulation of plasma osmotic pressure and transports endogenous and exogenous substances. The study undertaken to analyze the drug-binding mechanisms of HSA is crucial in understanding the bioavailability of drugs. In this study, we analyzed the cytotoxic activity of AsA on HepG2 (human hepatocellular carcinoma) cell lines and its binding, conformational, docking, molecular simulation studies with HSA under physiological pH 7.2.

Ligand Binding / Docking (Cont'd)

 β -Amyloid and Neprilysin Computational Studies Identify Critical Residues Implicated in Binding Specificity

Darrick Pope, Jeffrey D. Madura, Michael Cascio [Duquesne University]

J.Chem. Infor. and Mod. **54**, 1157–1165, 2014.

The zinc metalloprotease neprilysin (NEP) promiscuously degrades small bioactive peptides. NEP is among a select group of metalloenzymes that degrade the amyloid beta-peptide (A β) in vivo and in situ. Since accumulation of neurotoxic A β aggregates in the brain appears to be a causative agent in the pathophysiology of Alzheimer's disease (AD), increased clearance of A β resulting from overexpression of NEP exhibits therapeutic potential for AD. However, higher NEP peptidase activity may be harmful without an increased specificity for A β over other competing substrates.

Elucidating a Key Component of Cancer Metastasis: CXCL12 (SDF-1 α) Binding to CXCR4

Phanourios Tamamis , Christodoulos A. Floudas [Princeton University]

J.Chem. Infor. and Mod. **54**, 1174–1188, 2014.

The chemotactic signaling induced by the binding of chemokine CXCL12 (SDF-1 α) to chemokine receptor CXCR4 is of significant biological importance and is a potential therapeutic axis against HIV-1. However, as CXCR4 is overexpressed in certain cancer cells, the CXCL12: CXCR4 signaling is involved in tumor metastasis, progression, angiogenesis, and survival. Motivated by the pivotal role of the CXCL12: CXCR4 axis in cancer, we employed a comprehensive set of computational tools, predominantly based on free energy calculations and molecular dynamics simulations, to obtain insights into the molecular recognition of CXCR4 by CXCL12.

Computational Comparison of Imidazoline Association with the I2 Binding Site in Human Monoamine Oxidases

Livia Basile, Matteo Pappalardo, Salvatore Guccione [Università degli Studi di Catania], Danilo Milardi, Rona R. Ramsay

J.Chem. Infor. and Mod. **54**, 1200–1207, 2014.

Imidazoline ligands in I2-type binding sites in the brain alter monoamine turnover and release. One example of an I2 binding site characterized by binding studies, kinetics, and crystal structure has been described in monoamine oxidase B (MAO B). MAO A also binds imidazolines but has a different active site structure. Docking and molecular dynamics were used to explore how 2-(2-benzofuranyl)-2-imidazoline hydrochloride (2-BFI) binds to MAO A and to explain why tranlylcypromine increases tight binding to MAO B.

Key Binding and Susceptibility of NS3/4A Serine Protease Inhibitors against Hepatitis C Virus

Arthitaya Meeprasert, Supot Hannongbua, Thanyada Rungrotmongkol [Chulalongkorn University]

J.Chem. Infor. and Mod. **54**, 1208–1217, 2014.

Hepatitis C virus (HCV) causes an infectious disease that manifests itself as liver inflammation, cirrhosis, and can lead to the development of liver cancer. Its NS3/4A serine protease is a potent target for drug design and development since it is responsible for cleavage of the scissile peptide bonds in the polyprotein important for the HCV life cycle. Herein, the ligand-target interactions and the binding free energy of the four current NS3/4A inhibitors (boceprevir, telaprevir, danoprevir, and BI201335) were investigated by all-atom molecular dynamics simulations with three different initial atomic velocities.

Ligand Binding / Docking (Cont'd)

Charge Clamps of Lysines and Hydrogen Bonds Play Key Roles in the Mechanism to Fix Helix 12 in the Agonist and Antagonist Positions of Estrogen Receptor α : Intramolecular Interactions Studied by the Ab Initio Fragment Molecular Orbital Method

Chiduru Watanabe[Tokai University], Kaori Fukuzawa, Shigenori Tanaka, Sachiko Aida-Hyugaji

J. Phys. Chem. B., **118**, 4993–5008, 2014.

The mechanism to fix helix 12 (H12) in the agonist/antagonist position, which is involved in controlling transcriptional activation, of the human estrogen receptor α ligand binding domain (hER α LBD) is studied by using fragment molecular orbital calculations at the Møller–Plesset second-order perturbation levels to analyze inter-fragment interaction energies (IFIEs), electrostatic potentials (ESPs), and atomic charges. The mutually attractive and complementary relationships between H12 and highly conserved Lys529/Lys362 are shown through the IFIEs and ESPs.

Enzyme Catalysis

Rotation Triggers Nucleotide-Independent Conformational Transition of the Empty β Subunit of F1-ATPase

Jacek Czub, Helmut Grubmüller [Max Planck Institute for Biophysical Chemistry]

J. Am. Chem. Soc., 2013, **136**, 6960–6968, 2014.

F1-ATPase (F1) is the catalytic portion of ATP synthase, a rotary motor protein that couples proton gradients to ATP synthesis. These concerted transitions drive the synthesis of ATP from ADP and phosphate. Here, we study the coupling between the mechanical progression of γ and the conformations of $\alpha 3\beta 3$. Using molecular dynamics simulations, we show that the nucleotide-free β subunit, initially in the open, low-affinity state, undergoes a spontaneous closing transition to the half-open state in response to the γ rotation in the synthesis direction.

Exploring the Water-Binding Pocket of the Type II Dehydroquinase Enzyme in the Structure-Based Design of Inhibitors

Beatriz Blanco, Antía Sedes, Antonio Peón, José M. Otero, Mark J. van Raaij, Paul Thompson, Alastair R. Hawkins, Concepción González-Bello [Universidad de Santiago de Compostela]

J. Med. Chem., **57**, 3494–3510, 2014.

Structural and computational studies to explore the WAT1 binding pocket in the structure-based design of inhibitors against the type II dehydroquinase (DHQ2) enzyme are reported. The crystal structures of DHQ2 from *M. tuberculosis* in complex with four of the reported compounds are described. The electrostatic interaction observed between the guanidinium group of the essential arginine and the carboxylate group of one of the inhibitors in the reported crystal structures supports the recently suggested role of this arginine as the residue that triggers the release of the product from the active site.

Insight into the binding modes and inhibition mechanisms of adamantyl-based 1,3-disubstituted urea inhibitors in the active site of the human soluble epoxide hydrolase

Hang Chen, Ying Zhang, Chun Ye, Ting T. Feng, Ju G. Han [University of Science and Technology of China,]

J. Biomol. Stru. and Dyn., **32**, 1231–1247, 2014.

Soluble epoxide hydrolase (sEH) is a promising new target for treating hypertension and inflammation. Considerable efforts have been devoted to develop novel inhibitors. In this study, the binding modes and interaction mechanisms of a series of adamantyl-based 1,3-disubstituted urea inhibitors were investigated by molecular docking, molecular dynamics simulations, binding free energy calculations, and binding energy decomposition analysis. Based on binding affinity, the most favorable binding mode was determined for each inhibitor.

Enzyme Catalysis (Cont'd)

Conserved water-mediated recognition and dynamics of NAD⁺ (carboxamide group) to hIMPDPH enzyme: water mimic approach toward the design of isoform-selective inhibitor

Hridoy R. Bairagya, Deepak K. Mishra, Bishnu P. Mukhopadhyay [National Institute of Technology, Durgapur], K. Sekar

J. Biomol. Stru. and Dyn., 32, 1248-1262, 2014.

Inosine monophosphate dehydrogenase (IMPDPH) enzyme involves in GMP biosynthesis pathway. Type I hIMPDPH is expressed at lower levels in all cells, whereas type II is especially observed in acute myelogenous leukemia, chronic myelogenous leukemia cancer cells, and 10 ns simulation of the IMP-NAD⁺ complex structures (PDB ID. 1B3O and 1JCN) have revealed the presence of a few conserved hydrophilic centers near carboxamide group of NAD⁺. Three conserved water molecules (W1, W, and W1') in di-nucleotide binding pocket of enzyme have played a significant role in the recognition of carboxamide group (of NAD⁺) to D274 and H93 residues.

Molecular Dynamics Study of Helicobacter pylori Urease

Mona S. Minkara, Melek N. Ucisik, Michael N. Weaver, Kenneth M. Merz, Jr. [Michigan State University]

J. Chem. Theor. and Comp., 10, 1852–1862, 2014.

Helicobacter pylori have been implicated in an array of gastrointestinal disorders including, but not limited to, gastric and duodenal ulcers and adenocarcinoma. This bacterium utilizes an enzyme, urease, to produce copious amounts of ammonia through urea hydrolysis in order to survive the harsh acidic conditions of the stomach. Molecular dynamics (MD) studies on the H. pylori urease enzyme have been employed in order to study structural features of this enzyme that may shed light on the hydrolysis mechanism. A total of 400 ns of MD simulation time were collected and analyzed in this study.

How Accurate Are Transition States from Simulations of Enzymatic Reactions?

Dvir Doron, Amnon Kohen, Kwangho Nam, Dan Thomas Major [Bar-Ilan University]

J. Chem. Theor. and Comp., 10, 1863–1871 2014.

The rate expression of traditional transition state theory (TST) assumes no recrossing of the transition state (TS) and thermal quasi-equilibrium between the ground state and the TS. Currently, it is not well understood to what extent these assumptions influence the nature of the activated complex obtained in traditional TST-based simulations of processes in the condensed phase in general and in enzymes in particular. Here we scrutinize these assumptions by characterizing the TSs for hydride transfer catalyzed by the enzyme Escherichia coli dihydrofolate reductase obtained using various simulation approaches.

The C-terminal extension of human RTEL1, mutated in Hoyeraal-Hreidarsson syndrome, contains Harmonin-N-like domains

Guilhem Faure, Patrick Revy, Michael Schertzer, Arturo Londono-Vallejo, Isabelle Callebaut [Université Pierre et Marie Curie-Paris 6]

Proteins: Stru. Fun. & Bioinf., 82, 897–903, 2014.

Several studies have recently shown that germline mutations in RTEL1, an essential DNA helicase involved in telomere regulation and DNA repair, cause Hoyeraal-Hreidarsson syndrome (HHS), a severe form of dyskeratosis congenita. Using original new softwares, facilitating the delineation of the different domains of the protein and the identification of remote relationships for orphan domains, we outline here that the C-terminal extension of RTEL1, downstream of its catalytic domain and including several HHS-associated mutations, contains a yet unidentified tandem of harmonin-N-like domains, which may serve as a hub for partner interaction.

Enzyme Catalysis (Cont'd)

Hydrolysis of DFP and the Nerve Agent (S)-Sarin by DFPase Proceeds along Two Different Reaction Pathways: Implications for Engineering Bioscavengers

Troy Wymore [University of Tennessee], Martin J. Field, Paul Langan, Jeremy C. Smith, Jerry M. Parks

J. Phys. Chem. B., **118**, 4479–4489, 2014.

Organophosphorus (OP) nerve agents such as (S)-sarin are among the most highly toxic compounds that have been synthesized. Engineering enzymes that catalyze the hydrolysis of nerve agents (“bioscavengers”) is an emerging prophylactic approach to diminish their toxic effects. Although its native function is not known, diisopropyl fluorophosphatase (DFPase) from *Loligo vulgaris* catalyzes the hydrolysis of OP compounds. Here, we investigate the mechanisms of diisopropylfluorophosphate (DFP) and (S)-sarin hydrolysis by DFPase with quantum mechanical/molecular mechanical umbrella sampling simulations. We find that the mechanism for hydrolysis of DFP involves nucleophilic attack by Asp229 on phosphorus to form a pentavalent intermediate.

The Mechanism of Citryl-Coenzyme A Formation Catalyzed by Citrate Synthase

Alexey Aleksandrov, Elena Zvereva, Martin Field [Université Joseph Fourier - Grenoble I]

J. Phys. Chem. B., **118**, 4505–4513, 2014.

The enzyme citrate synthase is used by all living cells to catalyze the first step of the citric acid cycle. In this work, we have investigated the enolization and condensation steps catalyzed by citrate synthase, using *ab initio* (B3LYP/def2-TZVP and MP2/aug-cc-pVDZ) quantum chemical/molecular mechanical hybrid potentials in conjunction with reaction-path-location algorithms and molecular dynamics free energy simulations. The results of the latter indicate that the catalytic His238 residue is in its neutral form, and also argue strongly for the presence of a water molecule in the enzyme’s catalytic center. Such a water is observed in some, but not all, of the experimentally resolved structures of the protein.

Computational Evaluation of the Dynamic Fluctuations of Peripheral Loops Enclosing the Catalytic Tunnel of a Family 7 Cellobiohydrolase

David M. Granum, Timothy C. Schutt, C. Mark Maupin [Colorado School of Mines]

J. Phys. Chem. B., **118**, 5340–5349, 2014.

The size and character of the peripheral loops enclosing the active site for cellulase enzymes is believed to play a major role in dictating many critical enzymatic properties. For many cellulases it is observed that fully enclosed active sites forming a tunnel are more conducive to cellobiohydrolase activity and the ability to processively move along the substrate. Conversely, a more open active site groove is indicative of endoglucanase activity. For both cellobiohydrolases and endoglucanases, the loop regions have been implicated in the ability of the enzyme to bind substrate, influence the pKa of active site residues, modulate the catalytic activity, and influence thermal stability.

Protein-Protein Interactions

Algorithms and tools for protein–protein interaction networks clustering, with a special focus on population-based stochastic methods

Clara Pizzuti , Simona E. Rombo [University of Palermo]

Bioinformatics. **30**, 1343-1352, 2014.

Protein–protein interaction (PPI) networks are powerful models to represent the pairwise protein interactions of the organisms. Clustering PPI networks can be useful for isolating groups of interacting proteins that participate in the same biological processes or that perform together specific biological functions. Evolutionary orthologies can be inferred this way, as well as functions and properties of yet uncharacterized proteins. We present an overview of the main state-of-the-art clustering methods that have been applied to PPI networks over the past decade.

Molecular dynamics, dynamic site mapping, and highthroughput virtual screening on leptin and the Ob receptor as anti-obesity target

Marco Tutone, Licia Pantano, Antonino Lauria, Anna Maria Almerico [università di Palermo]

J. Mol.Mod., **20**, 2247, 2014.

Body weight control is a mechanism finely regulated by several hormonal, metabolic, and nervous pathways. The leptin receptor (Ob-R) is crucial for energy homeostasis and regulation of food uptake. Leptin is a 16 kDa hormone that is mainly secreted by fat cells into the bloodstream, and under normal circumstances, circulating levels are proportionate to the fat body mass. In this study, we performed protein-protein docking among the re-built crystal structure of leptin and leptin binding domain (LBD).

Structure-Based Multiscale Approach for Identification of Interaction Partners of PDZ Domains

Garima Tiwari , Debasisa Mohanty [National Institute of Immunology]

J.Chem. Infor. and Mod. **54**, 1143–1156, 2014.

PDZ domains are peptide recognition modules which mediate specific protein–protein interactions and are known to have a complex specificity landscape. We have developed a novel structure-based multiscale approach which identifies crucial specificity determining residues (SDRs) of PDZ domains from explicit solvent molecular dynamics (MD) simulations on PDZ–peptide complexes and uses these SDRs in combination with knowledge-based scoring functions for proteomewide identification of their interaction partners. Multiple explicit solvent simulations ranging from 5 to 50 ns duration have been carried out on 28 PDZ–peptide complexes with known binding affinities.

Intuitive, but not simple: Including explicit water molecules in protein–protein docking simulations improves model quality

Hardik I. Parikh , Glen E. Kellogg [Virginia Commonwealth University]

Proteins: Stru. Fun. & Bioinf., **82**, 916–932, 2014.

Characterizing the nature of interaction between proteins that have not been experimentally cocrystallized requires a computational docking approach that can successfully predict the spatial conformation adopted in the complex. In this work, the Hydropathic INTERactions (HINT) force field model was used for scoring docked models in a data set of 30 high-resolution crystallographically characterized “dry” protein–protein complexes and was shown to reliably identify native-like models.

Membrane Proteins and Lipid Peptide Interactions

Molecular Modeling of Lipid Membrane Curvature Induction by a Peptide: More than Simply Shape

Alexander J. Sodt [National Institutes of Health, Rockville] ,
Richard W. Pastor

Biophysical Journal. **106**, 1958-1969, 2014.

Molecular dynamics simulations of an amphipathic helix embedded in a lipid bilayer indicate that it will induce substantial positive curvature (e.g., a tube of diameter 20 nm at 16% surface coverage). The induction is twice that of a continuum model prediction that only considers the shape of the inclusion. The discrepancy is explained in terms of the additional presence of specific interactions described only by the molecular model. The conclusion that molecular shape alone is insufficient to quantitatively model curvature is supported by contrasting molecular and continuum models of lipids with large and small headgroups (choline and ethanolamine, respectively), and of the removal of a lipid tail (modeling a lyso-lipid).

A Bayesian statistical approach of improving knowledge-based scoring functions for protein–ligand interactions

Sam Z. Grinter , Xiaoqin Zou [University of Missouri]

J. Comp. Chem., **35**, 932–943, 2014.

Knowledge-based scoring functions are widely used for assessing putative complexes in protein–ligand and protein–protein docking and for structure prediction. Even with large training sets, knowledge-based scoring functions face the inevitable problem of sparse data. Here, we have developed a novel approach for handling the sparse data problem that is based on estimating the inaccuracies in knowledge-based scoring functions.

A balanced procedure for the treatment of cluster–ligand interactions on gold phosphine systems in catalysis

Doreen Mollenhauer [Victoria University of Wellington] , Nicola Gaston

J. Comp. Chem., **35**, 986–997, 2014.

The use of a dispersion correction to density functional calculations was found to be crucial for both structure optimization and the calculation of binding energies. We find that PBE-D3 performs well with a variation in energetics of 0.7–10.9 kcal/mol, PBE0-D3 better with 0.0–3.3 kcal/mol, and B2PLYP-D3 the best with 0.2–2.4 kcal/mol, when compared to the best available benchmark [CCSD(T) or SCS-MP2].

Molecular dynamics simulation of neuropeptide B and neuropeptide W in the dipalmitoylphosphatidylcholine membrane bilayer

Mahesh Chandra Patra, Jitendra Maharana [Orissa University of Agriculture and Technology], Sukanta Kumar Pradhan , Surya Narayan Rath

J. Biomol. Stru. and Dyn., **32**, 1118-1131, 2014.

GPR7 and GPR8 are recently orphanized G-protein-coupled receptors that are implicated in the regulation of neuroendocrine function, feeding behavior, and energy homeostasis. Neuropeptide B (NPB) and neuropeptide W (NPW) are two membrane-bound hypothalamic peptides, which specifically antagonize GPR7 and GPR8. Despite years of research, an accurate estimation of structure and molecular recognition of these neuropeptide systems still remains elusive. Herein, we investigated the structure, orientation, and interaction of NPB and NPW in a dipalmitoylphosphatidylcholine bilayer using long-range molecular dynamics (MD) simulation.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Improved Coarse-Grained Modeling of Cholesterol-Containing Lipid Bilayers

Michael D. Daily, Brett N. Olsen, Paul H. Schlesinger, Daniel S. Ory, Nathan A. Baker [Pacific Northwest National Laboratory]

J. Chem. Theor. and Comp, **10**, 2137–2150, 2014.

Cholesterol trafficking, which is an essential function in mammalian cells, is intimately connected to molecular-scale interactions through cholesterol modulation of membrane structure and dynamics and interaction with membrane receptors. Cholesterol has been shown experimentally to thicken the membrane and increase phospholipid tail order between 0 and 40% cholesterol, above which these effects plateau or slightly decrease. Here, we showed that the published MARTINI coarse-grained force-field for phospholipid (POPC) and cholesterol fails to capture these effects.

Sidekick for Membrane Simulations: Automated Ensemble Molecular Dynamics Simulations of Transmembrane Helices

Benjamin A. Hall, Khairul Bariyyah Abd Halim, Amanda Buyan, Beatrice Emmanouil, Mark S. P. Sansom [University of Oxford]

J. Chem. Theor. and Comp, **10**, 2165–2175, 2014.

The interactions of transmembrane (TM) α -helices with the phospholipid membrane and with one another are central to understanding the structure and stability of integral membrane proteins. These interactions may be analyzed via coarse grained molecular dynamics (CGMD) simulations. To obtain statistically meaningful analysis of TM helix interactions, large (N ca. 100) ensembles of CGMD simulations are needed. To facilitate the running and analysis of such ensembles of simulations, we have developed Sidekick, an automated pipeline software for performing high throughput CGMD simulations of α -helical peptides in lipid bilayer membranes.

Protonation of DMPC in a Bilayer Environment Using a Linear Response Approximation

Vitor H. Teixeira, Diogo Vila-Viçosa, António M. Baptista, Miguel Machuqueiro [Universidade de Lisboa]

J. Chem. Theor. and Comp, **10**, 2176–2184, 2014.

pH is a very important property, influencing all important biomolecules such as proteins, nucleic acids, and lipids. The effect of pH on proteins has been the subject of many computational works in recent years. However, the same has not been done for lipids, especially in their most biologically relevant environment: the bilayer. A reason for this is the inherent technical difficulty in dealing with this type of periodic systems. Here, we tackle this problem by developing a Poisson–Boltzmann-based method that takes in consideration the periodic boundary conditions of lipid bilayer patches.

Refined OPLS All-Atom Force Field for Saturated Phosphatidylcholine Bilayers at Full Hydration

Arkadiusz Maciejewski, Marta Pasenkiewicz-Gierula, Oana Cramariuc, Ilpo Vattulainen, Tomasz Rog [Tampere University of Technology]

J. Phys. Chem. B, **118**, 4571–4581, 2014.

In the present study, we determined the parameters for torsion angles in the phosphatidylcholine and glycerol moieties and in the acyl chains, as well the partial atomic charges. In these calculations, we used three methods: (1) Hartree–Fock (HF), (2) second order Møller–Plesset perturbation theory (MP2), and (3) density functional theory (DFT). We also tested the effect of the polar environment by using the polarizable continuum model (PCM), and for acyl chains the van der Waals parameters were also adjusted. In effect, six parameter sets were generated and tested on a DPPC bilayer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Characterization of the Immersion Properties of the Peripheral Membrane Anchor of the FATC Domain of the Kinase "Target of Rapamycin" by NMR, Oriented CD Spectroscopy, and MD Simulations

Lisa A. M. Sommer, J. Joel Janke, W. F. Drew Bennett, Jochen Bürck, Anne S. Ulrich, D. Peter Tieleman, Sonja A. Dames [Technische Universität München]

J. Phys. Chem. B., **118**, 4817–4831, 2014.

The immersion depth was characterized by NMR-monitored interaction studies with DPC micelles containing paramagnetically tagged 5- or 16-doxyl stearic acid (5-/16-SASL) and by analyzing the paramagnetic relaxation enhancement (PRE) from Mn²⁺ in the solvent. Complementary MD-simulations of micellar systems in the absence and presence of protein showed that 5-/16-SASL can move in the micelle and that 16-SASL can bend such that the doxyl group is close to the headgroup region and not deep in the interior as commonly assumed. Based on oriented CD (OCD) data, the single α -helix of oxidized/reduced y1fatc has an angle to the membrane normal of 30–60°/ 35–65° in neutral and 5–35°/ 0–30° in negatively charged bilayers.

Lipid Dynamics Studied by Calculation of 31P Solid-State NMR Spectra Using Ensembles from Molecular Dynamics Simulations

Sara K. Hansen, Mikkel Vestergaard, Lea Thøgersen, Birgit Schiøtt, Niels Chr. Nielsen, Thomas Vosegaard [Aarhus University]

J. Phys. Chem. B., **118**, 5119–5129, 2014.

We present a method to calculate 31P solid-state NMR spectra based on the dynamic input from extended molecular dynamics (MD) simulations. The dynamic information conferred by MD simulations is much more comprehensive than the information provided by traditional NMR dynamics models based on, for example, order parameters. Therefore, valuable insight into the dynamics of biomolecules may be achieved by the present method. We have applied this method to study the dynamics of lipid bilayers containing the antimicrobial peptide alamethicin, and we show that the calculated 31P spectra obtained with input from MD simulations are in agreement with experiments under a large range of different sample conditions, including vesicles and oriented samples with and without peptides.

Protein Folding

Salt effects on hydrophobic-core formation in folding of a helical miniprotein studied by molecular dynamics simulations

Takao Yoda[Nagahama Institute of Bio-Science and Technology], Yuji Sugita, Yuko Okamoto

Proteins: Stru. Fun. & Bioinf., **82**, 933–943, 2014.

We have investigated effects of salt ions on folding events of a helical miniprotein chicken villin headpiece subdomain HP36. Low concentrations of ions alter electrostatic interactions between charged groups of folding simulations of HP36 in explicit water solvent with or without ions. For efficient sampling of the conformational space of HP36, the multicanonical replica-exchange molecular dynamics method was employed. Our analyses suggest that salt alters salt-bridging nature of the protein at later stages of folding at room temperature.

Protein Folding (Cont'd)

Protein Folding Thermodynamics: A New Computational Approach

Song-Ho Chong , Sihyun Ham [Sookmyung Women's University]

J. Phys. Chem. B., **118**, 5017–5025, 2014.

Folding free energy is the fundamental thermodynamic quantity characterizing the stability of a protein. Yet, its accurate determination based on computational techniques remains a challenge in physical chemistry. A straightforward brute-force approach would be to conduct molecular dynamics simulations and to estimate the folding free energy from the equilibrium population ratio of the unfolded and folded states. However, this approach is not sensible at physiological conditions where the equilibrium population ratio is vanishingly small: it is extremely difficult to reliably obtain such a small equilibrium population ratio due to the low rate of folding/unfolding transitions. We present such an approach that focuses on the probability distributions of the effective energy (solvent-averaged protein potential energy) in the folded and unfolded states.

Evidence for the Sequential Folding Mechanism in RNase H from an Ensemble-Based Model

Abhishek Narayan , Athi N. Naganathan [Indian Institute of Technology Madras]

J. Phys. Chem. B., **118**, 5050–5058, 2014.

In our current work, we provide computational evidence for this unique folding mechanism by employing a structure-based statistical mechanical model. Upon calibrating the energetic terms of the model with equilibrium measurements, we predict multiple intermediate states in the folding of RNase H that closely resemble experimental observations. Remarkably, a simplified landscape representation adequately captures the folding complexity and predicts the possibility of a well-defined sequence of folding events.

Nucleic Acids

Understanding the Mechanical Properties of DNA Origami Tiles and Controlling the Kinetics of Their Folding and Unfolding Reconfiguration

Haorong Chen, Te-Wei Weng, Molly M. Riccitelli, Yi Cui, Joseph Irudayaraj, Jong Hyun Choi [Purdue University]

J. Am. Chem. Soc., 2013, **136**, 6995–7005, 2014.

DNA origami represents a class of highly programmable macromolecules that can go through conformational changes in response to external signals. Here we show that a two-dimensional origami rectangle can be effectively folded into a short, cylindrical tube by connecting the two opposite edges through the hybridization of linker strands and that this process can be efficiently reversed via toehold-mediated strand displacement. The reconfiguration kinetics was experimentally studied as a function of incubation temperature, initial origami concentration, missing staples, and origami geometry. A kinetic model was developed by introducing the j factor to describe the reaction rates in the cyclization process.

Nucleic Acids (Cont'd)

Electrostatic map of T7 DNA: comparative analysis of functional and electrostatic properties of T7 RNA polymerase-specific promoters

S.G. Kamzolova, P.M. Beskaravainy, A.A. Osypov, T.R. Dzhelebin, E.A. Temlyakova & A.A. Sorokin [Institute of Cell Biophysics, RAS]

J. Biomol. Stru. and Dyn., 32, 1184-1192, 2014.

The entire T7 bacteriophage genome contains 39937 base pairs (Database NCBI RefSeq N1001604). Here, electrostatic potential distribution around double helical T7 DNA was calculated by Coulomb method using the computer program of Sorokin A.A. (lptolik@gmail.com). Electrostatic profiles of 17 promoters recognized by T7 phage-specific RNA polymerase were analyzed.

Molecular simulation investigation on the interaction between barrier-to-autointegration factor or its Gly25Glu mutant and DNA

Yu-Dong Shang, Ji-Long Zhang, Hong-Xing Zhang, Qing-Chuan Zheng [Jilin University]

J. Mol. Mod., 20, 2246, 2014.

In order to understand the binding mechanism between Barrier-to-autointegration factor (BAF) and DNA, two DNA:BAF complexes with wild type (WT) BAF and its Gly25Glu point mutate type (MT) were generated by molecular docking on the basis of the crystal structures of BAF (PDB code: 2ODG, chain A) and DNA (PDB code: 2BZF, chain B and C). Then, molecular dynamics (MD) simulations were performed on the two docked structures, as well as BAF (WT) and BAF (MT). The results show that monomer BAF is more flexible than BAF in DNA:BAF complex, suggesting that DNA is effective to stabilize conformation of BAF, which is in good agreement with the experimental results.

2. METHODOLOGY

Quantitative Structure-Activity Relations

QSARINS-chem: Insubria datasets and new QSAR/QSPR models for environmental pollutants in QSARINS

Paola Gramatica [University of Insubria], Stefano Cassani, Nicola Chirico

J. Comp. Chem., 35, 1036–1044, 2014.

A database of environmentally hazardous chemicals, collected and modeled by QSAR by the Insubria group, is included in the updated version of QSARINS, software recently proposed for the development and validation of QSAR models by the genetic algorithm-ordinary least squares method. In this version, a module, named QSARINS-Chem, includes several datasets of chemical structures and their corresponding endpoints (physicochemical properties and biological activities). The chemicals are accessible in different ways (CAS, SMILES, names and so forth) and their three-dimensional structure can be visualized.

Quantitative Structure-Activity Relations (Cont'd)

Global Quantitative Structure-Activity Relationship Models vs Selected Local Models as Predictors of Off-Target Activities for Project Compounds

Robert P. Sheridan [Merck Research Laboratories]

J.Chem. Infor. and Mod. **54**, 1083–1092, 2014.

In the pharmaceutical industry, it is common for large numbers of compounds to be tested for off-target activities. Given a compound synthesized for an on-target project P, what is the best way to predict its off-target activity X? Is it better to use a global quantitative structure-activity relationship (QSAR) model calibrated against all compounds tested for X, or is it better to use a local model for X calibrated against only the set of compounds in project P? The literature is not consistent on this topic, and strong claims have been made for either. One particular idea is that local models will be superior to global models in prospective prediction if one generates many local models and chooses the type of local model that best predicts recent data.

Beyond the Scope of Free-Wilson Analysis. 2: Can Distance Encoded R-Group Fingerprints Provide Interpretable Nonlinear Models?

Mats Eriksson, Hongming Chen, Lars Carlsson, J. Willem M. Nissink, John G. Cumming, Ingemar Nilsson [Global Safety Assessment]

J.Chem. Infor. and Mod. **54**, 1117–1128, 2014.

In a recent study, we presented a novel quantitative-structure-activity-relationship (QSAR) approach, combining R-group signatures and nonlinear support-vector-machines (SVM), to build interpretable local models for congeneric compound sets. Here, we outline further refinements in the fingerprint scheme for the purpose of analyzing and visualizing structure-activity relationships (SAR). The concept of distance encoded R-group signature descriptors is introduced, and we explore the influence of different signature encoding schemes on both interpretability and predictive power of the SVM models using ten public data sets

Quantitative Structure-Activity Relationship Models of Chemical Transformations from Matched Pairs Analyses

Jeremy M. Beck , Clayton Springer [Novartis Institutes for BioMedical Research]

J.Chem. Infor. and Mod. **54**, 1226–1234, 2014.

The concepts of activity cliffs and matched molecular pairs (MMP) are recent paradigms for analysis of data sets to identify structural changes that may be used to modify the potency of lead molecules in drug discovery projects. Here we present an alternative technique that determines pairwise descriptors for each matched pair and then uses a QSAR model to estimate the activity change associated with a chemical transformation. The descriptors effectively group similar transformations and incorporate information about the transformation and its local environment. Use of a transformation QSAR model allows one to estimate the activity change for novel transformations and therefore returns predictions for a larger fraction of test set compounds.

Potentials and Parameters

Conformational Preferences of Modified Uridines: Comparison of AMBER Derived Force Fields

Indrajit Deb, Joanna Sarzynska, Lennart Nilsson, Ansuman Lahiri [University of Calcutta]

J.Chem. Infor. and Mod. **54**, 1129–1142, 2014.

In this work, we tested these parameters on a set of modified uridine residues, namely, dihydrouridine, 2-thiouridine, 4-thiouridine, pseudouridine, and uridine-5-oxyacetic acid, by performing molecular dynamics and replica exchange molecular dynamics simulations of these nucleosides. Although our simulations using the FF99 force field did not, in general, reproduce the experimentally observed conformational characteristics well, combination of the parameter set with recent revisions of the FF99 force field for RNA showed noticeable improvement for some of the nucleosides.

Prediction of hydration free energies for the SAMPL4 diverse set of compounds using molecular dynamics simulations with the OPLS-AA force field

Oliver Beckstein [Arizona State University], Anaïs Fourier, Bogdan I. Iorga

J. Comp. Aided. Mol. Design, **28**, 265-276 2014.

All-atom molecular dynamics computer simulations were used to blindly predict the hydration free energies of a range of small molecules as part of the SAMPL4 challenge. Compounds were parametrized on the basis of the OPLS-AA force field using three different protocols for deriving partial charges: (1) using existing OPLS-AA atom types and charges with minor adjustments of partial charges on equivalent connecting atoms and derivation of new parameters for a number of distinct chemical groups (N-alkyl imidazole, nitrate) that were not present in the published force field; (2) calculation of quantum mechanical charges via geometry optimization, followed by electrostatic potential (ESP) fitting, using Jaguar at the LMP2/cc-pVTZ(-F) level; and (3) via geometry optimization and CHelpG charges, followed by two-stage RESP fitting.

Molecular Dynamics

Interaction of 2-APB, dantrolene, and TDMT with IP3R and RyR modulates ER stress-induced programmed cell death I and II in neuron-like PC12 cells: an experimental and computational investigation

Niloufar Ansari, Hamid Hadi-Alijanvand, Marjan Sabbaghian, Mahmoud Kiaei, Fariba Khodaghohi [Shahid Beheshti University of Medical Sciences]

J. Biomol. Stru. and Dyn., **32**, 1211-1230, 2014.

Ca²⁺ is an essential second messenger, playing a fundamental role in maintaining cell viability and neuronal activity. Two specific endoplasmic reticulum calcium channels, ryanodine receptors (RyRs) and inositol 1,4,5-trisphosphate receptors (IP₃Rs) play an important role in Ca²⁺ regulation. In the present study, we provided a 3D structure of RyR and IP₃R by homology modeling, and we predicted their interactions with a known neuroprotective compound, 3-thiomethyl-5,6-(dimethoxyphenyl)-1,2,4-triazine (TDMT), as well as two inhibitors, dantrolene and 2-aminoethoxydiphenyl borate (2-APB).

Molecular Dynamics (Cont'd)

A Method for Creating Thermal and Angular Momentum Fluxes in Nonperiodic Simulations

Kelsey M. Stocker , J. Daniel Gezelter [University of Notre Dame]

J. Chem. Theor. and Comp, **10**, 1878–1886, 2014.

We present a new reverse nonequilibrium molecular dynamics method that can be used with nonperiodic simulation cells. This method applies thermal and/or angular momentum fluxes between two arbitrary regions of the simulation and is capable of creating stable temperature and angular velocity gradients while conserving total energy and angular momentum. One particularly useful application is the exchange of kinetic energy between two concentric spherical regions, which can be used to generate thermal transport between nanoparticles and the solvent that surrounds them.

Molecular Dynamics of the Proline Switch and Its Role in Crk Signaling

Junchao Xia , Ronald M. Levy [the State University of New Jersey]

J. Phys. Chem. B., **118**, 4535–4545, 2014.

The Crk adaptor proteins play a central role as a molecular timer for the formation of protein complexes including various growth and differentiation factors. A self-regulatory mechanism for Crk was recently proposed, which involves domain–domain rearrangement. It is initiated by a cis–trans isomerization of a specific proline residue (Pro238 in chicken Crk II) and can be accelerated by Cyclophilin A. To understand how the proline switch controls the autoinhibition at the molecular level, we performed large-scale molecular dynamics and metadynamics simulations in the context of short peptides and multidomain constructs of chicken Crk II.

Free Energy Perturbation

Prediction of free energies of hydration with COSMO-RS on the SAMPL4 data set

Jens Reinisch [COSMOlogic GmbH&CoKG], Andreas Klamt

J. Comp. Aided. Mol. Design, **28**, 169-173, 2014.

The COSMO-RS method has been used for the prediction of free energies of hydration on a dataset of 47 complex multifunctional compounds considered in the SAMPL4 challenge. Straight application of the COSMOtherm software with the parameterization C21_0108 yields a predictive accuracy of 1.46 kcal/mol root mean square error overall and 1.18 kcal/mol if a single dominant outlier is removed.

Extended solvent-contact model approach to SAMPL4 blind prediction challenge for hydration free energies

Hwangseo Park [Sejong University]

J. Comp. Aided. Mol. Design, **28**, 175-186, 2014.

Extended solvent-contact model was applied to the blind prediction of the hydration free energies of 47 organic molecules included in the SAMPL4 data set. To obtain a suitable prediction tool, we constructed a hydration free energy function involving three kinds of atomic parameters. With respect to total 34 atom types introduced to describe all SAMPL4 molecules, 102 atomic parameters were defined and optimized with a standard genetic algorithm in such a way to minimize the difference between the experimental hydration free energies and those calculated with the hydration free energy function.

Free Energy Perturbation (Cont'd)

Extensive all-atom Monte Carlo sampling and QM/MM corrections in the SAMPL4 hydration free energy challenge

Samuel Genheden [University of Southampton], Ana I. Cabedo Martinez, Michael P. Criddle, Jonathan W. Essex

J. Comp. Aided. Mol. Design, **28**, 187-200, 2014.

We present our predictions for the SAMPL4 hydration free energy challenge. Extensive all-atom Monte Carlo simulations were employed to sample the compounds in explicit solvent. While the focus of our study was to demonstrate well-converged and reproducible free energies, we attempted to address the deficiencies in the general Amber force field force field with a simple QM/MM correction. We show that by using multiple independent simulations, including different starting configurations, and enhanced sampling with parallel tempering, we can obtain well converged hydration free energies.

The SAMPL4 hydration challenge: evaluation of partial charge sets with explicit-water molecular dynamics simulations

Hari S. Muddana, Neil V. Sapra, Andrew T. Fenley, Michael K. Gilson [University of California San Diego]

J. Comp. Aided. Mol. Design, **28**, 277-287, 2014.

We used blind predictions of the 47 hydration free energies in the SAMPL4 challenge to test multiple partial charge models in the context of explicit solvent free energy simulations with the general AMBER force field. One of the partial charge models, IPolQ-Mod, is a fast continuum solvent-based implementation of the IPolQ approach. The AM1-BCC, restrained electrostatic potential (RESP) and IPolQ-Mod approaches all perform reasonably well ($R^2 > 0.8$), while VCharge, though faster, gives less accurate results (R^2 of 0.5). The AM1-BCC results are more accurate than those of RESP for tertiary amines and nitrates, but the overall difference in accuracy between these methods is not statistically significant.

QM and QM/MM

fireball/amber: An Efficient Local-Orbital DFT QM/MM Method for Biomolecular Systems

Jesús I. Mendieta-Moreno, Ross C. Walker, James P. Lewis, Paulino Gómez-Puertas, Jesús Mendieta, José Ortega [Universidad Autónoma de Madrid]

J. Chem. Theor. and Comp, **10**, 2185–2193, 2014.

In recent years, quantum mechanics/molecular mechanics (QM/MM) methods have become an important computational tool for the study of chemical reactions and other processes in biomolecular systems. In the QM/MM technique, the active region is described by means of QM calculations, while the remainder of the system is described using a MM approach. Because of the complexity of biomolecules and the desire to achieve converged sampling, it is important that the QM method presents a good balance between accuracy and computational efficiency. Here, we report on the implementation of a QM/MM technique that combines a DFT approach specially designed for the study of complex systems using first-principles molecular dynamics simulations (FIREBALL) with the AMBER force fields and simulation programs.

 QM and QM/MM (Cont'd)

Computational Screening of Weak Hydrogen Bond Networks: Predicting Stable Structures for Difluoromethane Oligomers

Giacomo Prampolini, Laura Carbonaro, Gang Feng, Luca Evangelisti, Walther Caminati, Ivo Cacelli [Istituto di Chimica dei Composti OrganoMetallici (ICCOM-CNR)]

J. Chem. Theor. and Comp, **10**, 2204–2211, 2014.

The stability and the structure of small difluoromethane oligomers are studied by combining classical Monte Carlo and quantum mechanical calculations. A hierarchical procedure was adopted to validate the accuracy of the whole protocol: the force field used in Monte Carlo simulations is parametrized on the basis of dimer intermolecular energies computed with density functional theory. The density functional is similarly chosen by comparing the interaction energies with reference values, purposely computed at a coupled cluster level, extrapolated at the complete basis set.

Predicting hydration free energies with a hybrid QM/MM approach: an evaluation of implicit and explicit solvation models in SAMPL4

Gerhard König [National Institutes of Health, National Heart, Lung and Blood Institute], Frank C. Pickard IV, Ye Mei, Bernard R. Brooks

J. Comp. Aided. Mol. Design, **28**, 245–257, 2014.

In this context, the method is referred to as QM-NBB. Based on snapshots from MM sampling and accounting for their correct Boltzmann weight, it is possible to obtain hydration free energies that incorporate the effect of solute entropy. We evaluate the performance of several QM implicit solvent models, as well as explicit solvent QM/MM for the blind subset of the SAMPL4 hydration free energy challenge. While classical free energy simulations with molecular dynamics give root mean square deviations (RMSD) of 2.8 and 2.3 kcal/mol, the hybrid approach yields an improved RMSD of 1.6 kcal/mol.

QM/MM study of the C—C coupling reaction mechanism of CYP121, an essential Cytochrome p450 of Mycobacterium tuberculosis

Victoria G. Dumas, Lucas A. Defelipe, Ariel A. Petruk, Adrian G. Turjanski, Marcelo A. Marti [Universidad de Buenos Aires,]

Proteins: Stru. Fun. & Bioinf., **82**, 1004–1021, 2014.

Among 20 p450s of Mycobacterium tuberculosis (Mt), CYP121 has received an outstanding interest, not only due to its essentiality for bacterial viability but also because it catalyzes an unusual carbon–carbon coupling reaction. In the present work we have used classical and quantum based computer simulation methods to study in detail its reaction mechanism. Our results show that substrate binding promotes formation of the initial oxy complex, Compound I is the responsible for first Tyr radical formation, and that the second Tyr radical is formed subsequently, through a PCET reaction, promoted by the presence of key residue Arg386. The final C—C coupling reaction possibly occurs in bulk solution, thus yielding the product in one oxygen reduction cycle.

QM/MM Free-Energy Simulations of Reaction in Serratia marcescens Chitinase B Reveal the Protonation State of Asp142 and the Critical Role of Tyr214

Jitrayut Jitonnorn [University of Bristol], Michael A. L. Limb, Adrian J. Mulholland

J. Phys. Chem. B., **118**, 4771–4783, 2014.

Serratia marcescens Chitinase B (ChiB), belonging to the glycosidase family 18 (GH18), catalyzes the hydrolysis of β -1,4-glycosidic bond, with retention of configuration, via an unusual substrate-assisted mechanism, in which the substrate itself acts as an intramolecular nucleophile. Here, both elementary steps (glycosylation and deglycosylation) of the ChiB-catalyzed reaction are investigated by means of combined quantum mechanics/molecular mechanics (QM/MM) umbrella sampling molecular dynamics (MD) simulations at the SCC-DFTB/CHARMM22 level of theory.

QM and QM/MM (Cont'd)

Quantum Mechanics/Molecular Mechanics Study of Oxygen Binding in Hemocyanin

Toru Saito , Walter Thiel [Max-Planck-Institut für Kohlenforschung]

J. Phys. Chem. B., **118**, 5034–5043, 2014.

We report a combined quantum mechanics/molecular mechanics (QM/MM) study on the mechanism of reversible dioxygen binding in the active site of hemocyanin (Hc). The QM region is treated by broken-symmetry density functional theory (DFT) with spin projection corrections. The X-ray structures of deoxygenated (deoxyHc) and oxygenated (oxyHc) hemocyanin are well reproduced by QM/MM geometry optimizations. The computed relative energies strongly depend on the chosen density functional.

Vapor Pressures and Heats of Sublimation of Crystalline β -Cellobiose from Classical Molecular Dynamics Simulations with Quantum Mechanical Corrections

Jakob Wohlerl [KTH Royal Institute of Technology]

J. Phys. Chem. B., **118**, 5365–5373, 2014.

In this paper, we report the calculation of the enthalpy of sublimation, Δ_{subH} , as a function of temperature of crystalline β -cellobiose from molecular dynamics (MD) simulations, using two popular carbohydrate force fields. Together with the entropy difference between the solid and the vapor, ΔS , evaluated at atmospheric pressure, Δ_{subH} gives the vapor pressure of cellobiose over the solid phase as a function of T . It is found that when quantum mechanical corrections to the enthalpy calculated from the distribution of normal modes is applied both force fields give Δ_{subH} close to experiments.

MD and QM/MM Studies on Long-Chain L- α -Hydroxy Acid Oxidase: Substrate Binding Features and Oxidation Mechanism

Yang Cao, Shuang Han, Lushan Yu, Haiyan Qian, Jian-Zhong Chen [Zhejiang University]

J. Phys. Chem. B., **118**, 5406–5417, 2014.

Long-chain L- α -hydroxy acid oxidase (LCHAO) is a flavin mononucleotide (FMN)-dependent oxidase that dehydrogenates L- α -hydroxy acids to keto acids. There were two different mechanisms, named as hydride transfer (HT) mechanism and carbanion (CA) mechanism, respectively, proposed about the catalytic process for the FMN-dependent L- α -hydroxy acid oxidases on the basis of biochemical data. However, crystallographic and kinetic studies could not provide enough evidence to prove one of the mechanisms or eliminate the alternative. In the present studies, theoretical computations were carried out to study the molecular mechanism for LCHAO-catalyzed dehydrogenation of L-lactate.

Ligand Docking

Thienoquinolines as Novel Disruptors of the PKC ϵ /RACK2 Protein–Protein Interaction

Florian Rechfeld, Peter Gruber, Johannes Kirchmair, Markus Boehler, Nina Hauser, Georg Hechenberger, Dorota Garczarczyk, Gennady B. Lapa, Maria N. Preobrazhenskaya, Peter Goekjian, Thierry Langer, Johann Hofmann [Innsbruck Medical University]

J. Med. Chem., **57**, 3235–3246, 2014.

Ten protein kinase C (PKC) isozymes play divergent roles in signal transduction. Because of sequence similarities, it is particularly difficult to generate isozyme-selective small molecule inhibitors. In order to identify such a selective binder, we derived a pharmacophore model from the peptide EAVSLKPT, a fragment of PKC ϵ that inhibits the interaction of PKC ϵ and receptor for activated C-kinase 2 (RACK2). A database of 330 000 molecules was screened in silico, leading to the discovery of a series of thienoquinolines that disrupt the interaction of PKC ϵ with RACK2 in vitro.

Ligand Docking (Cont'd)

Pharmacophoric Modifications Lead to Superpotent $\alpha\text{v}\beta 3$ Integrin Ligands with Suppressed $\alpha 5\beta 1$ Activity

Stefanie Neubauer, Florian Rechenmacher, Richard Brimiouille, Francesco Saverio Di Leva, Alexander Bochen, Tariq R. Sobahi, Margret Schottelius, Ettore Novellino, Carlos Mas-Moruno, Luciana Marinelli, Horst Kessler [Technische Universität München]

J. Med. Chem., **57**, 3410–3417, 2014.

The selective targeting of the $\alpha\text{v}\beta 3$ integrin subtype without affecting the structurally closely related receptor $\alpha 5\beta 1$ is crucial for understanding the details of their biological and pathological functions and thus of great relevance for diagnostic and therapeutic approaches in cancer treatment. Here, we present the synthesis of highly active RGD peptidomimetics for the $\alpha\text{v}\beta 3$ integrin with remarkable selectivity against $\alpha 5\beta 1$. Incorporation of a methoxypyridine building block into a ligand scaffold and variation of different functional moieties led to $\alpha\text{v}\beta 3$ -antagonistic activities in the low nanomolar or even subnanomolar range.

On-the-Fly Learning and Sampling of Ligand Binding by High-Throughput Molecular Simulations

S. Doerr, G. De Fabritiis [Universitat Pompeu Fabra]

J. Chem. Theor. and Comp., **10**, 2064–2069, 2014.

High-throughput molecular dynamics (MD) simulations are a computational method consisting of using multiple short trajectories, instead of few long ones, to cover slow biological time scales. Compared to long trajectories this method offers the possibility to start the simulations in successive batches, building a knowledgeable model of the available data to inform subsequent new simulations iteratively. Here, we demonstrate an automatic, iterative, on-the-fly method for learning and sampling molecular simulations in the context of ligand binding for the case of trypsin–benzamidine binding.

Efficient Characterization of Protein Cavities within Molecular Simulation Trajectories: trj_cavity

Teresa Paramo, Alexandra East, Diana Garzón, Martin B. Ulmschneider, Peter J. Bond [University of Cambridge]

J. Chem. Theor. and Comp., **10**, 2151–2164, 2014.

Protein cavities and tunnels are critical in determining phenomena such as ligand binding, molecular transport, and enzyme catalysis. MD simulations enable the exploration of the flexibility and conformational plasticity of protein cavities, extending the information available from static experimental structures relevant to, for example, drug design. Here, we present a new tool implemented within the GROMACS framework for the rapid identification and characterization of cavities detected within MD trajectories.

Intermolecular Potential for Binding of Protonated Peptide Ions with Perfluorinated Hydrocarbon Surfaces

Subha Pratihari, Swapnil C. Kohale, Saulo A. Vázquez, William L. Hase [Texas Tech University]

J. Phys. Chem. B., **118**, 5577–5588, 2014.

An analytic potential energy function was developed to model both short-range and long-range interactions between protonated peptide ions and perfluorinated hydrocarbon chains. The potential function is defined as a sum of two-body potentials of the Buckingham form. The parameters of the two-body potentials were obtained by fits to intermolecular potential energy curves calculated for CF₄, which represents the F and C atoms of a perfluoroalkane chain, interacting with small molecules chosen as representatives of the main functional groups and atoms present in protonated peptide ions: specifically, CH₄, NH₃, NH₄⁺, and HCOOH.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 50, May, 2014.

- 50-60 **MaterialVis: Material visualization tool using direct volume and surface rendering techniques** ,Erhan Okuyan, Uğur Güdükbay [Bilkent University], Ceyhun Bulutay, Karl-Heinz Heinig

Visualization of the materials is an indispensable part of their structural analysis. We developed a visualization tool for amorphous as well as crystalline structures, called *MaterialVis*.

- 61-70 **Molecular dynamics simulations of mutated Mycobacterium tuberculosis L-alanine dehydrogenase to illuminate the role of key residues** ,Baoping Ling [Qufu Normal University], Siwei Bi, Min Sun, Zhihong Jing, Xiaoping Li, Rui Zhang

See Applications / Enzyme Catalysis.

- 71-77 **Solvent effect on the crystal morphology of 2,6-diamino-3,5-dinitropyridine-1-oxide: A molecular dynamics simulation study** ,Wenyan Shi [Nanjing University of Science & Technology], Mingzhu Xia, Wu Lei, Fengyun Wang

The attachment energy (AE) calculations were performed to predict the growth morphology of 2,6-diamino-3,5-dinitropyridine-1-oxide (ANPyO) in vacuum. The molecular dynamics (MD) method was applied to simulate the interaction of trifluoroacetic acid solvent with the habit faces and the corrected AE model was adopted to predict the growth habit of ANPyO in the solvent.

- 78-89 **Study on the disulfide bond and disulfide loop of native and mutated SOD1 protein** ,S.P. Keerthana, P. Kolandaivel [Bharathiar University]

See Applications / Protein Structure Analysis.

- 90-99 **Theoretical investigation on gas-phase reaction of CF₃CH₂OCH₃ with OH radicals and fate of alkoxy radicals (CF₃CH(O.)OCH₃/CF₃CH₂OCH₂O.)** ,Bhupesh Kumar Mishra, Makroni Lily, Ramesh Chandra Deka, Asit K. Chandra [North-Eastern Hill University]

Detailed theoretical investigation has been performed on the mechanism, kinetics and thermochemistry of the gas phase reactions of CF₃CH₂OCH₃ (HFE-263fb2) with OH radicals using *ab-initio* and DFT methods.

- 100-112 **In silico design of small molecule inhibitors of CDK9/cyclin T1 interaction** , Jelena Randjelovic, Slavica Eric, Vladimir Savic [University of Belgrade]

See Applications / Protein Dynamics.

- 113-124 **Effect of D23N mutation on the dimer conformation of amyloid β -proteins: Ab initio molecular simulations in water**, Akisumi Okamoto, Atsushi Yano, Kazuya Nomura, Shin'ichi Higai, Noriyuki Kurita [Toyohashi University of Technology]

See Applications / Protein Structure Analysis.

- 125-133 **Computational study of protein secondary structure elements: Ramachandran plots revisited**, Francisco Carrascoza ["Babes-Bolyai" University], Snezana Zaric, Radu Silaghi-Dumitrescu

Potential energy surface (PES) were built for nineteen amino acids using density functional theory (PW91 and DFT M062X/6-311**). Examining the energy as a function of the ϕ/ψ dihedral angles in the allowed regions of the Ramachandran plot, amino acid groups that share common patterns on their PES plots and global minima were identified.

- 134-141 **Voxel based parallel post processor for void nucleation and growth analysis of atomistic simulations of material fracture**, H. Hemani, M. Warrier, N. Sakthivel, S. Chaturvedi [Bhabha Atomic Research Centre]

Molecular dynamics (MD) simulations are used in the study of void nucleation and growth in crystals that are subjected to tensile deformation. These simulations are run for typically several hundred thousand time steps depending on the problem.

- 142-151 **Molecular dynamics analysis of the interaction between the human BCL6 BTB domain and its SMRT, NcoR and BCOR corepressors: The quest for a consensus dynamic pharmacophore**, J.M. Granadino-Roldán [Universidad de Jaén], C. Obiol-Pardo, M. Pinto, A. Garzón, J. Rubio-Martínez

See Applications / Ligand Binding.

Journal of Computational Chemistry, 35(12), May, 2014.

- 891–903 **Towards the design of novel boron- and nitrogen-substituted ammonia-borane and bifunctional arene ruthenium catalysts for hydrogen storage**, Sateesh Bandaru, Niall J. English [University College Dublin], Andrew D. Phillips, J.M.D. MacElroy

Electronic-structure density functional theory calculations have been performed to construct the potential energy surface for H₂ release from ammonia-borane, with a novel bifunctional cationic ruthenium catalyst based on the sterically bulky β -diketiminate ligand (Schreiber et al., ACS Catal. 2012, 2, 2505).

- 904–909 **Exchange coupling and magnetic anisotropy in a family of bipyrimidyl radical-bridged dlanthanide complexes: Density functional theory and *ab initio* calculations**, Yi-Quan Zhang [Nanjing Normal University], Cheng-Lin Luo and Qiang Zhang

The origin of the magnetic anisotropy energy barriers in a series of bpym^{•−} (bpym = 2,2'-bipyrimidine) radical-bridged dlanthanide complexes [(Cp*₂Ln)₂(μ -bpym)]⁺ [Cp* = pentamethylcyclopentadienyl; Ln = Gd^{III} (1), Tb^{III} (2), Dy^{III} (3), Ho^{III} (4), Er^{III} (5)] has been explored using density functional theory (DFT) and *ab initio* methods.

- 910–922 **Cooperativity and cluster growth patterns in acetonitrile: A DFT study** ,Karunakaran Remya , Cherumuttathu H. Suresh [CSIR-National Institute for interdisciplinary Science and Technology]

Cooperativity in intermolecular interactions and cluster growth patterns of acetonitrile has been studied using M06L density functional theory. Cyclic, ladder-type, stacked, cross-stacked, and mixed patterns are studied.

- 923–931 **Metallophilic interaction in gold halide: Quantum chemical study of AuX (X = F — at)** ,Xinying Li [Henan University]

Quantum chemical calculations of the structures, stabilities, and metallophilic interactions of AuX halides (X = F — At) at the CCSD(T) theoretical level with extended basis sets were performed.

- 932–943 **A Bayesian statistical approach of improving knowledge-based scoring functions for protein–ligand interactions** ,Sam Z. Grinter , Xiaoqin Zou [University of Missouri]

See Applications / Membrane Proteins and Lipid-Peptide Interaction.

- 944–949 **How much tetraradical character is present in the Si₆Ge₉ cluster?** ,David Casanova [Basque Foundation for Science, Bilbao]

This study discusses in detail the supposedly tetraradicaloid nature of a spirobis(pentagerma[1.1.1]propellane) derivative recently reported by Ito et al. (J. Am. Chem. Soc., 2013, 135, 6770).

- 950–956 **Rapid determination of RMSDs corresponding to macromolecular rigid body motions** , Petr Popov ,Sergei Grudin [INRIA Grenoble—Rhône-Alpes]

Finding the root mean sum of squared deviations (RMSDs) between two coordinate vectors that correspond to the rigid body motion of a macromolecule is an important problem in structural bioinformatics, computational chemistry, and molecular modeling. Here, we present *RigidRMSD*, a new algorithm that determines a set of RMSDs corresponding to a set of rigid body motions of a macromolecule in constant time with respect to the number of atoms in the molecule.

- 957–963 **ST-analyzer: A web-based user interface for simulation trajectory analysis** ,Jong Cheol Jeong, Sunhwan Jo, Emilia L. Wu, Yifei Qi, Viviana Monje-Galvan, Min Sun Yeom, Lev Gorenstein, Feng Chen, Jeffery B. Klauda , Wonpil Im [The University of Kansas]

See Applications / Bioinformatics.

Journal of Computational Chemistry, 35(13), May, 2014.

- 965–977 **Investigation of the distinction between van der Waals interaction and chemical bonding based on the PAEM-MO diagram** ,Dong-Xia Zhao , Zhong-Zhi Yang [Liaoning Normal University]

In recent years, the basic problem of understanding chemical bonding, nonbonded, and/or van der Waals interactions has been intensively debated in terms of various theoretical methods. We propose and construct the potential acting on one electron in a molecule-molecular orbital (PAEM-MO) diagram, which draws the PAEM inserted the MO energy levels with their major atomic orbital components.

- 978–985 **Electronegativity estimator built on QTAIM-based domains of the bond electron density** ,David Ferro-Costas, Ignacio Pérez-Juste ,Ricardo A. Mosquera [Universidade de Vigo]

The electron localization function, natural localized molecular orbitals, and the quantum theory of atoms in molecules have been used all together to analyze the bond electron density (BED) distribution of different hydrogen-containing compounds through the definition of atomic contributions to the bonding regions. A function, g_{AH} , obtained from those contributions is analyzed along the second and third periods of the periodic table.

- 986–997 **A balanced procedure for the treatment of cluster–ligand interactions on gold phosphine systems in catalysis** ,Doreen Mollenhauer [Victoria University of Wellington] ,Nicola Gaston

See Applications / Membrane Proteins and Lipid-Peptide Interaction.

- 998–1009 **The reactions of $\text{Cr}(\text{CO})_6$, $\text{Fe}(\text{CO})_5$, and $\text{Ni}(\text{CO})_4$ with O_2 yield viable oxo-metal carbonyls** ,Zhi Sun, Henry F. Schaefer III, Yaoming Xie, Yongdong Liu[Beijing University of Technology], Rugang Zhong

Transition metal complexes with terminal oxo and dioxygen ligands exist in metal oxidation reactions, and many are key intermediates in various catalytic and biological processes. The prototypical oxo-metal $[(\text{OC})_5\text{Cr}=\text{O}$, $(\text{OC})_4\text{Fe}=\text{O}$, and $(\text{OC})_3\text{Ni}=\text{O}]$ and dioxygen-metal carbonyls $[(\text{OC})_5\text{Cr}=\text{OO}$, $(\text{OC})_4\text{Fe}=\text{OO}$, and $(\text{OC})_3\text{Ni}=\text{OO}]$ are studied theoretically.

- 1010–1023 **Extraction of site–site bridge functions and effective pair potentials from simulations of polar molecular liquids** ,Gennady N. Chuev [Russian Academy of Science, Pushchino], Ivan Vyalov , Nikolaj Georgi

We develop an efficient method to extract site–site bridge functions from molecular simulations. The method is based on the inverse solution of the reference site interaction model.

- 1024–1035 **Free energy calculations, enhanced by a gaussian ansatz, for the “chemical work” distribution** Georgios C. Boulougouris [Democritus University]

The evaluation of the free energy is essential in molecular simulation because it is intimately related with the existence of multiphase equilibrium. Recently, it was demonstrated that it is possible to evaluate the Helmholtz free energy using a single statistical ensemble along an entire isotherm by accounting for the “chemical work” of transforming each molecule, from an interacting one, to an ideal gas. In this work, we show that it is possible to perform such a free energy perturbation over a liquid vapor phase transition.

- 1036–1044 **QSARINS-chem: Insubria datasets and new QSAR/QSPR models for environmental pollutants in QSARINS** ,Paola Gramatica [University of Insubria], Stefano Cassani ,Nicola Chirico

See Methodology / Quantitative Structure–Activity Relations.

Journal of Computational Chemistry, 35(14), May, 2014.

- 1045–1057 **Quantitative investigation of bonding characteristics in ternary Zintl anions: Charge and energy analysis of $[\text{Sn}_2\text{E}^{15}_2(\text{ZnPh})]^-$ ($\text{E}^{15} = \text{Sb}, \text{Bi}$) and $[\text{Sn}_2\text{Sb}_5(\text{ZnPh})_2]^{3-}$** , Marc Raupach, Stefanie Dehnen, Ralf Tonner [Philipps-Universität Marburg]

The analysis of chemical bonding in Zintl anions and complexes thereof is mostly based on frontier molecular orbital (FMO) analysis. While this approach delivers remarkable insights, it falls short of providing quantitative measures for chemical bonding in these compounds. Here, we investigate the organozinc-ligated Zintl anions $[\text{Sn}_2\text{E}^{15}_2(\text{ZnPh})]^-$ ($\text{E}^{15} = \text{Sb}, \text{Bi}$) and $[\text{Sn}_2\text{Sb}_5(\text{ZnPh})_2]^{3-}$ with charge and energy analysis methods.

- 1058–1063 **Oxygen adsorption characteristics on hybrid carbon and boron-nitride nanotubes**, Haining Liu, C. Heath Turner [The University of Alabama]

In this work, first-principles density functional theory (DFT) is used to predict oxygen adsorption on two types of hybrid carbon and boron-nitride nanotubes (CBNNTs), zigzag (8,0), and armchair (6,6).

- 1064–1072 **Midpoint cell method for hybrid (MPI+OpenMP) parallelization of molecular dynamics simulations**, Jaewoon Jung, Takaharu Mori, Yuji Sugita [RIKEN Theoretical Molecular Science Laboratory]

See Applications / Bioinformatics.

- 1073–1081 **Assessment of the orbital-optimized coupled-electron pair theory for thermochemistry and kinetics: Improving on CCSD and CEPA(1)**, Emine Soydaş, Uğur Bozkaya [Atatürk University]

An assessment of the orbital-optimized coupled-electron pair theory [or simply “optimized CEPA(0),” OCEPA(0)] [Bozkaya and Sherrill, *J. Chem. Phys.* 2013, 139, 054104] for thermochemistry and kinetics is presented.

- 1082–1092 **A new perspective of shape recognition to discover the phase transition of finite-size clusters**, Po-Jen Hsu [National Central University]

An ultrafast shape-recognition technique was used to analyze the phase transition of finite-size clusters, which, according to our research, has not yet been accomplished.

- 1093–1100 **Reactivity index based on orbital energies**, Takao Tsuneda [University of Yamanashi], Raman K. Singh

This study shows that the chemical reactivities depend on the orbital energy gaps contributing to the reactions. In the process where a reaction only makes progress through charge transfer with the minimal structural transformation of the reactant, the orbital energy gap gradient (OEGG) between the electron-donating and electron-accepting orbitals is proven to be very low.

- 1101–1105 **ALMOST: An all atom molecular simulation toolkit for protein structure determination**, Biao Fu, Aleksandr B. Sahakyan, Carlo Camilloni, Gian Gaetano Tartaglia, Emanuele Paci, Amedeo Caflisch, Michele Vendruscolo, Andrea Cavalli [University of Cambridge]

See Applications / Bioinformatics.

Journal of Molecular Modeling, 20 (5), May, 2014.

- 2247 **Molecular dynamics, dynamic site mapping, and highthroughput virtual screening on leptin and the Ob receptor as anti-obesity target** ,Marco Tutone, Licia Pantano, Antonino Lauria, Anna Maria Almerico [università di Palermo]

See Applications / protein Protein Interactions.

- 2246 **Molecular simulation investigation on the interaction between barrier-to-autointegration factor or its Gly25Glu mutant and DNA** ,Yu-Dong Shang, Ji-Long Zhang, Hong-Xing Zhang, Qing-Chuan Zheng [Jilin University]

See Applications / Nucleic Acids.

- 2243 **Theoretical investigation of a “turn-on” fluorescent sensor induced by complexation of mercury(II) ion** ,Yong Xia, Zhengjian Qi [Southeast University], Yueming Sun, Du Cao, Huanhuan Ling, Fan Yang, Xin Ji

A selective $\text{Hg}^{2+}/\text{Cu}^{2+}$ -induced OFF-ON-OFF type of signaling pattern was calculated by density functional theory and time-dependent density functional theory method.

- 2242 **Geometries, stabilities and electronic properties of beryllium-silicon Be_2Si_n clusters** ,Shuai Zhang, Jing-He Wu, Jia-Wu Cui, Cheng Lu [Nanyang Normal University], Pan-Pan Zhou, Zhi-Wen Lu, Gen-Quan Li

The equilibrium geometries, growth patterns, stabilities, and electronic properties of bimetallic Be_2Si_n ($n = 1-11$) clusters are systematically investigated at the B3LYP/6-311G(d) level of theory.

- 2238 **Adsorption of 2,3,7,8-tetrochlorodibenzo-p-dioxins on intrinsic, defected, and Ti (N, Ag) doped graphene: a DFT study** ,Hongping Zhang, Weidong He [University of Electronic Science and Technology of China (UESTC)], Xuegang Luo, Xiaoyan Lin, Xiong Lu

In this study, density functional theory (DFT) method was applied to systematically investigate the interactions between TCDD and different types of graphene samples.

- 2236 **Fosfomycin Induced Structural Change in Fosfomycin Resistance Kinases FomA: Molecular Dynamics and Molecular Docking Studies** ,Yun-Jian Wu, Qing-Chuan Zheng, Ji-Long Zhang, Wen-Ting Chu, Ying-Lu Cui, Yan Wang, Hong-Xing Zhang [Jilin University]

See Applications / Protein Conformational Analysis.

- 2235 **Theoretical investigations on the enhancing effect of the cation- π interaction on the halogen bond in the $\text{M}\cdots\text{HCCX}\cdots\text{NH}_3$ ($\text{M} = \text{Li}^+, \text{Na}^+, \text{Cu}^+, \text{Ag}^+, \text{Au}^+$; $\text{X} = \text{Cl}, \text{Br}$) complexes** ,Dianguo Geng [Zibo Vocational Institute]

The $M\cdots HCCX\cdots NH_3$ ($M = Li^+, Na^+, Cu^+, Ag^+, Au^+$; $X = Cl, Br$) complexes were designed to study the influence of cation- π interaction on the $X\cdots N$ halogen bonds under M05-2X/aug-cc-pVDZ(PP) level.

- 2233 **Modeling the mechanism of action of lycopene as a hydroxyl radical scavenger**, Ajit Kumar Prasad, Phool C. Mishra [Banaras Hindu University]

The anti-oxidant action of lycopene as a hydroxyl radical scavenger through hydrogen abstraction and addition reaction mechanisms has been investigated. Geometries of seven different conformations of lycopene were optimized employing density functional theory in gas phase which was followed by treatment of their solvation in aqueous media.

- 2230 **First-principles vdW-DF study on the enhanced hydrogen storage capacity of Pt-adsorbed grapheme**, Azadeh Khosravi, Abdolhosein Fereidoon, Morteza Ghorbanzadeh Ahangari, Masoud Darvish Ganji [Islamic Azad University], Seyed Negar Emami

Ab initio vdW calculations with the DFT level of theory were used to investigate hydrogen (H_2) adsorption on Pt-adsorbed graphene (Pt-graphene). We have explored the most energetically favorable sites for single Pt atom adsorption on the graphene surface.

- 2223 **Impact sensitivity and crystal lattice compressibility/free space**, Peter Politzer [University of New Orleans], Jane S. Murray

There is considerable evidence, which we discuss, indicating that compressibility and available free space in the crystal lattice are among the factors that govern the sensitivity of an explosive compound. Expanding and extending earlier work, we demonstrate, for 25 explosives, that there is an overall general tendency for greater impact sensitivity as the estimated free space per molecule increases.

- 2219 **Does cation break the cyano bond? A critical evaluation of nitrile-cation interaction**, Pei Meng Woi [University of Malaya], Maizathul Akmal A. Bakar, Ahmad Nazmi Rosli, Vannajan Sanghiran Lee, Mohd Rais Ahmad, Sharifuddin Md Zain, Yatimah Alias

DFT and G4 results reveal that cations display the following trends in imparting its positive charge to acrylonitrile; $H^+ > Li^+ > Na^+ > K^+$ for group I and $Be^{2+} > Mg^{2+} > Ca^{2+}$ for group II. Solvation by water molecules and interaction with cation make the cyano bond more polarized and exhibits ketene-imine character.

- 2217 **Long wavelength absorbing carbostyrils as test cases for different TDDFT procedures and solvent models**, Anne-Marie Kelterer [Graz University of Technology], Georg Uray, Walter M. F. Fabian

The vertical excitation energies of 3,4-dicyano-6-methoxy and 3,4-dicyano-6,7-dimethoxy carbostyryl have been computed with different approximations for the time-dependent density functional theory (TD-DFT) procedure and with different implementations of the continuum solvation model COSMO.

- 2216 **Discovery of in silico hits targeting the nsP3 macro domain of chikungunya virus**, Phuong T. V. Nguyen, Haibo Yu, Paul A. Keller [University of Wollongong]

The recent emergence and re-emergence of alphaviruses, in particular the chikungunya virus (CHIKV), in numerous countries has invoked a worldwide threat to human health, while simultaneously generating an economic burden on affected countries. This study reports on the discovery of potential inhibitors for the nsP3

macro domain of CHIKV using molecular docking, virtual screening, and molecular dynamics simulations, as well as work done to evaluate and confirm the active site of nsP3.

- 2213 **Computational investigations on the electronic and structural properties of the unsaturated silylenoid HP=SiLiF** ,Yuhua Qi [University of Jinan], Jing Ma, Chongjuan Xu, Bing Geng, Maoxia He

The structures of unsaturated silylenoid HP=SiLiF were studied by density functional theory at the B3LYP/6-311+G(d,P) level.

- 2208 **Multiconfigurational character of the ground states of polycyclic aromatic hydrocarbons. A systematic study** ,Ana E. Torres, Patricia Guadarrama, Serguei Fomine [Universidad Nacional Autónoma de México]

A systematic study of the electronic structure of polycyclic hydrocarbons from naphthalene to a system containing 80 fused benzene has been carried out.

- 2191 **Combined structure- and ligand-based pharmacophore modeling and molecular dynamics simulation studies to identify selective inhibitors of MMP-8** ,Sukesh Kalva, D. Vinod, Lilly M. Saleena [SRM University]

See Applications / Medicinal Chemistry and Drug Design.

- 2186 **A theoretical and experimental evaluation of imidazolium-based ionic liquids for atmospheric mercury capture** ,Cristina Iuga [Universidad Autónoma Metropolitana-Xochimilco], Corina Solís, J. Raúl Alvarez-Idaboy, Miguel Ángel Martínez, Ma. Antonieta Mondragón, Annik Vivier-Bunge

In this work, the capacity of three different imidazolium-based ionic liquids (ILs) for atmospheric mercury capture has been evaluated. Theoretical calculations using monomer and dimer models of ILs showed that [BMIM]⁺[SCN]⁻ and [BMIM]⁺[Cl]⁻ ionic liquids capture gaseous Hg⁰, while [BMIM]⁺[PF₆]⁻ shows no ability for this purpose.

- 2181 **DFT study of the Lewis acid mediated synthesis of 3-acyltetramic acids** ,Hannes Mikula [Vienna University of Technology], Dennis Svatunek, Philipp Skrinjar, Ernst Horkel, Christian Hametner, Johannes Fröhlich

The synthesis of 3-acyltetramic acids by C-acylation of pyrrolidine-2,4-diones was studied by density functional theory (DFT). DFT was applied to the mycotoxin tenuazonic acid (TeA), an important representative of these bioactive natural compounds.

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Vol. 23, No. 5

June, 2014

Coverage Period: June 2014

About 100 Papers from more than 30 Journals are cited.

1	APPLICATIONS (76)	Page 2		
1.1	Small Molecules (16)			
	Water and Solvation	Page 2	QSAR	Page 5
	Med. Chem. And Drug Design	Page 3		
1.2	Biopolymers (60)			
	Bioinformatics and Cheminformatics	Page 6	Ligand Binding	Page 13
	Protein Secondary Structure	Page 8	Enzyme Catalysis	Page 13
	Protein Conformational Analysis	Page 9	Protein-Protein Interactions	Page 16
	Protein Structure Analysis	Page 10	Membrane Proteins	Page 17
	Protein Dynamics	Page 11	Protein Folding	Page 19
	Free Energy Calculations	Page 13	Nucleic Acids	Page 20
1.3	Polymers			
1.4	Surfaces, Catalysts and Material	Page 22		
2	METHODOLOGY (22)	Page 22		
	QSAR	Page 22	Comparative or Homology	Page 26
	Potentials and Parameters	Page 23	Ligand Docking	Page 26
	QM & QM/MM	Page 24		
3	JOURNAL REVIEWS (5)	Page 29		
	Journal of Molecular Graphics and Modeling, 51, June, 2014.			
	Journal of Computational Chemistry, 35 (15), June, 2014.			
	Journal of Computational Chemistry, 35 (16), June, 2014..			
	Journal of Computational Chemistry, 35 (17), June, 2014.			
	Journal of Molecular Modeling, 20 (6), June, 2014.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 43		
5	COPYRIGHT, DISCLAIMER AND PUBLISHER INFORMATION			

1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Effect of explicit water molecules on ligand-binding affinities calculated with the MM/GBSA approach

Paulius Mikulskis, Samuel Genheden, Ulf Ryde [Lund University]

J. Mol. Mod., **20**, 2273, 2014.

We tested different approaches to including the effect of binding-site water molecules for ligand-binding affinities within the MM/GBSA approach (molecular mechanics combined with generalised Born and surface-area solvation). As a test case, we studied the binding of nine phenol analogues to ferritin. The effect of water molecules mediating the interaction between the receptor and the ligand can be studied by considering a few water molecules as a part of the receptor. We extended previous methods by allowing for a variable number of water molecules in the binding site.

WATsite: Hydration site prediction program with PyMOL interface

Bingjie Hu, Markus A. Lill [Purdue University]

J. Comp. Chem., **35**, 1255–1260, 2014.

Water molecules that mediate protein–ligand interactions or are released from the binding site on ligand binding can contribute both enthalpically and entropically to the free energy of ligand binding. To elucidate the thermodynamic profile of individual water molecules and their potential contribution to ligand binding, a hydration site analysis program WATsite was developed together with an easy-to-use graphical user interface based on PyMOL. WATsite identifies hydration sites from a molecular dynamics simulation trajectory with explicit water molecules.



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Medicinal Chemistry and Drug Design

Identification of a high affinity selective inhibitor of Polo-like kinase 1 for cancer chemotherapy by computational approach

Manoj Kumar, Sai Prasad Pydi, Sujata Sharma, Tej P. Singh, Punit Kaur[All India Institute of Medical Sciences, New Delhi]

J. Mol.Graph. and Mod., **51**, 104-112, 2014.

Polo-like kinase (Plk)1 is a key regulator of the cell cycle during mitotic phase and is an attractive anti-mitotic drug target for cancer. Plk1 is a member of Ser/Thr kinase family which also includes Plk2-4 in human. Plk1 promotes the cell division whereas Plk2 and Plk3 are reported to act as tumour suppressors. The available inhibitors of Plk1 also suppress Plk2 and Plk3 activity significantly resulting in the cell death of normal cells in addition to the cancer cells. Hence, it is imperative to explore Plk1 specific inhibitors as anti-cancer drugs. In this work, a selective potential inhibitor of Plk1 has been identified by molecular docking based high throughput virtual screening.

Inhibitor Design Strategy Based on an Enzyme Structural Flexibility: A Case of Bacterial MurD Ligase

Andrej Perdih[Freie Universität Berlin], Martina Hrast, Hélène Barreteau, Stanislav Gobec, Gerhard Wolber, Tom Solmajer

J.Chem. Infor. and Mod. **54**, 1451–1466, 2014.

Increasing bacterial resistance to available antibiotics stimulated the discovery of novel efficacious antibacterial agents. The biosynthesis of the bacterial peptidoglycan, where the MurD enzyme is involved in the intracellular phase of the UDP-MurNAc-pentapeptide formation, represents a collection of highly selective targets for novel antibacterial drug design. In our previous computational studies, the C-terminal domain motion of the MurD ligase was investigated using Targeted Molecular Dynamic (TMD) simulation and the Off-Path Simulation (OPS) technique. In this study, we present a drug design strategy using multiple protein structures for the identification of novel MurD ligase inhibitors.

Prediction of Linear Cationic Antimicrobial Peptides Based on Characteristics Responsible for Their Interaction with the Membranes

Boris Vishnepolsky, Malak Pirtskhalava [I. Beritashvili Center of Experimental Biomedicine]

J.Chem. Infor. and Mod. **54**, 1512–1523 6, 2014.

Most available antimicrobial peptides (AMP) prediction methods use common approach for different classes of AMP. Contrary to available approaches, we suggest that a strategy of prediction should be based on the fact that there are several kinds of AMP that vary in mechanisms of action, structure, mode of interaction with membrane, etc. According to our suggestion for each kind of AMP, a particular approach has to be developed in order to get high efficacy. Consequently, in this paper, a particular but the biggest class of AMP, linear cationic antimicrobial peptides (LCAP), has been considered and a newly developed simple method of LCAP prediction described.

Medicinal Chemistry and Drug Design (Cont'd)

Identification and Validation of Novel PERK Inhibitors

Qiantao Wang, Jihyun Park, Ashwini K. Devkota, Eun Jeong Cho, Kevin N. Dalby, Pengyu Ren [The University of Texas at Austin]

J.Chem. Infor. and Mod. **54**, 1467–1475, 2014.

PERK, as one of the principle unfolded protein response signal transducers, is believed to be associated with many human diseases, such as cancer and type-II diabetes. There has been increasing effort to discover potent PERK inhibitors due to its potential therapeutic interest. In this study, a computer-based virtual screening approach is employed to discover novel PERK inhibitors, followed by experimental validation. Using a focused library, we show that a consensus approach, combining pharmacophore modeling and docking, can be more cost-effective than using either approach alone.

Site-Identification by Ligand Competitive Saturation (SILCS) assisted pharmacophore modeling

Wenbo Yu, Sirish Kaushik Lakkaraju, E. Prabhu Raman, Alexander D. MacKerell Jr.[University of Maryland]

J. Comp. Aided. Mol. Design, **28**, 491-507, 2014.

Database screening using receptor-based pharmacophores is a computer-aided drug design technique that uses the structure of the target molecule (i.e. protein) to identify novel ligands that may bind to the target. Typically receptor-based pharmacophore modeling methods only consider a single or limited number of receptor conformations and map out the favorable binding patterns in vacuum or with a limited representation of the aqueous solvent environment, such that they may suffer from neglect of protein flexibility and desolvation effects.

Molecular dynamics modeling the synthetic and biological polymers interactions pre-studied via docking

Vladimir B. Tsvetkov, Alexander V. Serbin [Biomodulators and Drugs Research Center, Health RDF]

J. Comp. Aided. Mol. Design, **28**, 647-673, 2014.

In previous works we reported the design, synthesis and in vitro evaluations of synthetic anionic polymers modified by alicyclic pendant groups (hydrophobic anchors), as a novel class of inhibitors of the human immunodeficiency virus type 1 (HIV-1) entry into human cells. Recently, these synthetic polymers interactions with key mediator of HIV-1 entry-fusion, the tri-helix core of the first heptad repeat regions [HR1]₃ of viral envelope protein gp41, were pre-studied via docking in terms of newly formulated algorithm for stepwise approximation from fragments of polymeric backbone and side-group models toward real polymeric chains. In the present article the docking results were verified under molecular dynamics (MD) modeling. In the present article the docking results were verified under molecular dynamics (MD) modeling.

Decoding the structural events in substrate-gating mechanism of eukaryotic prolyl oligopeptidase using normal mode analysis and molecular dynamics simulations

Swati Kaushik, Catherine Etchebest, Ramanathan Sowdhamini [Tata Institute of Fundamental Research]

Proteins: Stru. Fun. & Bioinf., **82**, 1428–1443, 2014.

Prolyl oligopeptidase (POP) is a serine protease, unique for its ability to cleave various small oligopeptides shorter than 30 amino acids. POP is an important drug target since it is implicated in various neurological disorders. Here, we have used normal mode analysis and molecular dynamics to unravel the mechanism of substrate entry in mammalian POPs, which has been debated until now. Motions observed using normal modes of porcine and bacterial POPs were analyzed and compared, augmented by molecular dynamics of these proteins.

Medicinal Chemistry and Drug Design (Cont'd)

Virtual screening of traditional Chinese medicine (TCM) database: identification of fragment-like lead molecules for filariasis target asparaginyl-tRNA synthetase

Hemant Arya, Mohane Selvaraj Coumar [Pondicherry University]

J. Mol.Mod., **20**, 2266, 2014.

Lymphatic filariasis (LF) is a vector borne infectious disease caused by the nematode *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. Over 120 million people are affected by LF in the world, of which two-thirds are in Asia. In this study, asparaginyl-tRNA synthetase (AsnRS; PDB ID: 2XGT) essential for the protein bio-synthesis in the filarial nematode was used to carry out virtual screening (VS) of plant constituents from traditional Chinese medicine (TCM) database. Docking as well as E-pharmacophore based VS were carried out to identify the hits.

Theoretical insight into the mechanism for the inhibition of the cysteine protease cathepsin B by 1,2,4-thiadiazole derivatives

Mauricio Angel Vega-Tejido [Universidad de la República], Sarah El Chamy Maluf, Camila Ramalho Bonturi, Julio Ricardo Sambrano, Oscar N. Ventura

J. Mol.Mod., **20**, 2254, 2014.

Several cellular disorders have been related to the overexpression of the cysteine protease cathepsin B (CatB), such as rheumatic arthritis, muscular dystrophy, osteoporosis, Alzheimer's disease, and tumor metastasis. In this work, we present molecular modeling and docking studies of a series of eight 1,2,4-thiadiazole compounds. Substitutions at two positions (3 and 5) on the 1,2,4-thiadiazole ring were analyzed, and the docking scores were correlated to experimental data. Substitutions at two positions (3 and 5) on the 1,2,4-thiadiazole ring were analyzed, and the docking scores were correlated to experimental data.

Quantitative Structure-Activity Relations

Design of novel camphane-based derivatives with antimycobacterial activity

Georgi Stavrakov, Violeta Valcheva, Irena Philipova, Irini Doytchinova [Medical University of Sofia]

J. Mol.Graph. and Mod., **51**, 7-12, 2014.

Although tuberculosis (TB) continues to be one of the leading infectious disease killers globally, it is curable and preventable. We reported for a new class of anti-TB agents – camphane-based derivatives with nanomolar activity against *Mycobacterium tuberculosis* strains. The quantitative structure–activity relationship (QSAR) study on 12 compounds revealed several structural requirements for antimycobacterial activity: two hydrogen bond donors, two or three rings and no large branched substituents. Here, we describe the design of a set of nine novel camphane-based derivatives following these requirements.

Quantity Structure-Activity Relations (Cont'd)

Atom-based 3D-QSAR, molecular docking and molecular dynamics simulation assessment of inhibitors for thyroid hormone receptor α and β

Manish Kumar Gupta [Chhatrapati Shahu Ji Maharaj University], Krishna Misra

J. Mol.Mod., **20**, 2286, 2014.

The three-dimensional quantitative structure–activity relationship (3D-QSAR) for inhibitors of thyroid hormone receptors (TR) α and (TR) β was studied. Molecular docking explained the conformations of molecules and important amino acid residues at the docking pocket, and a molecular dynamics simulation study further uncovered the binding process and validated the rationality of docking results. The findings not only lead to a better understanding of interactions between these antagonists and thyroid hormone receptors α and β , but also provide valuable information about the impact of structure on activity that will be very beneficial in the design of novel antagonists with preferred activity.

QSPR ensemble modelling of the 1:1 and 1:2 complexation of Co^{2+} , Ni^{2+} , and Cu^{2+} with organic ligands: relationships between stability constants

Vitaly Solov'ev [Russian Academy of Sciences], Alexandre Varnek, Aslan Tsivadze

J. Comp. Aided. Mol. Design, **28**, 549-564, 2014.

Quantitative structure–property relationship (QSPR) modeling of stability constants for the metal:ligand ratio 1:1 ($\log K$) and 1:2 ($\log \beta_2$) complexes of 3 transition metal ions with diverse organic ligands in aqueous solution was performed using ensemble multiple linear regression analysis and substructural molecular fragment descriptors. The modeling was performed on the sets containing 396 and 132 (Co^{2+}), 613 and 233 (Ni^{2+}), 883 and 257 (Cu^{2+}) $\log K$ and $\log \beta_2$ values, respectively. The models have been validated in external fivefold cross-validations procedure as well as on the external test set containing new ligands recently reported in the literature.

1.2. Biopolymers

Bioinformatics and Cheminformatics

SKINK: a web server for string kernel based kink prediction in α -helices

Tim Seifert, Andreas Lund, Benny Kneissl [Pharma Research and Early Development Informatics (pREDi)], Sabine C. Mueller, Christofer S. Tautermann, Andreas Hildebrandt

Bioinformatics, **30**, 1769-1770, 2014.

The reasons for distortions from optimal α -helical geometry are widely unknown, but their influences on structural changes of proteins are significant. Hence, their prediction is a crucial problem in structural bioinformatics. Here, we present a new web server, called SKINK, for string kernel based kink prediction. Extending our previous study, we also annotate the most probable kink position in a given α -helix sequence..

Bioinformatics and Cheminformatics (Cont'd)

The Application of Statistical Methods to Cognate Docking: A Path Forward?

Paul C. D. Hawkins [OpenEye Scientific Software, 9 Bisbee Court], Brian P. Kelley, and Gregory L. Warren

J.Chem. Infor. and Mod. **54**, 1339–1355, 2014.

Cognate docking has been used as a test for pose prediction quality in docking engines for decades. In this paper, we report a statistically rigorous analysis of cognate docking performance using tools in the OpenEye docking suite. We address a number of critically important aspects of the cognate docking problem that are often handled poorly: data set quality, methods of comparison of the predicted pose to the experimental pose, and data analysis. The focus of the paper lies in the third problem, extracting maximally predictive knowledge from comparison data.

An Unbiased Method To Build Benchmarking Sets for Ligand-Based Virtual Screening and its Application To GPCRs

Jie Xia, Hongwei Jin, Zhenming Liu, Liangren Zhang, Xiang Simon Wang [Howard University]

J.Chem. Infor. and Mod. **54**, 1433–1450, 2014.

Benchmarking data sets have become common in recent years for the purpose of virtual screening, though the main focus had been placed on the structure-based virtual screening (SBVS) approaches. Due to the lack of crystal structures, there is great need for unbiased benchmarking sets to evaluate various ligand-based virtual screening (LBVS) methods for important drug targets such as G protein-coupled receptors (GPCRs). Herein, we propose an unbiased method to build benchmarking sets for LBVS and validate it on a multitude of GPCRs targets.

Applicability Domain Analysis (ADAN): A Robust Method for Assessing the Reliability of Drug Property Predictions

Pau Carrió, Marta Pinto, Gerhard Ecker, Ferran Sanz, Manuel Pastor [Universitat Pompeu Fabra]

J.Chem. Infor. and Mod. **54**, 1500–1511, 2014.

We report a novel method called ADAN (Applicability Domain ANalysis) for assessing the reliability of drug property predictions obtained by in silico methods. The assessment provided by ADAN is based on the comparison of the query compound with the training set, using six diverse similarity criteria. For every criterion, the query compound is considered out of range when the similarity value obtained is larger than the 95th percentile of the values obtained for the training set. The final outcome is a number in the range of 0–6 that expresses the number of unmet similarity criteria and allows classifying the query compound within seven reliability categories.

MLP Tools: a PyMOL plugin for using the molecular lipophilicity potential in computer-aided drug design

Nils Oberhauser, Alessandra Nurisso[University of Lausanne], Pierre-Alain Carrupt

J. Comp. Aided. Mol. Design, **28**, 587-596, 2014.

The molecular lipophilicity potential (MLP) is a well-established method to calculate and visualize lipophilicity on molecules. We are here introducing a new computational tool named *MLP Tools*, written in the programming language Python, and conceived as a free plugin for the popular open source molecular viewer PyMOL. The plugin is divided into several sub-programs which allow the visualization of the MLP on molecular surfaces, as well as in three-dimensional space in order to analyze lipophilic properties of binding pockets.

Bioinformatics and Cheminformatics (Cont'd)

The MoSGrid Science Gateway – A Complete Solution for Molecular Simulations

Jens Krüger [University of Tübingen], Richard Grunzke, Sandra Gesing, Sebastian Breuers, André Brinkmann, Luis de la Garza, Oliver Kohlbacher, Martin Kruse, Wolfgang E. Nagel, Lars Packschies, Ralph Müller-Pfefferkorn, Patrick Schäfer, Charlotta Schärfe, Thomas Steinke, Tobias Schlemmer, Klaus Dieter Warzecha, Andreas Zink, Sonja Herres-Pawlis

J. Chem. Theor. and Comp., **10**, 2232–2245, 2014.

The MoSGrid portal offers an approach to carry out high-quality molecular simulations on distributed compute infrastructures to scientists with all kinds of background and experience levels. A user-friendly Web interface guarantees the ease-of-use of modern chemical simulation applications well established in the field. The usage of well-defined workflows annotated with metadata largely improves the reproducibility of simulations in the sense of good lab practice. The MoSGrid science gateway supports applications in the domains quantum chemistry (QC), molecular dynamics (MD), and docking.

PAIRpred: Partner-specific prediction of interacting residues from sequence and structure

Fayyaz ul Amir Afsar Minhas, Brian J. Geiss, Asa Ben-Hur [Colorado State University]

Proteins: Stru. Fun. & Bioinf., **82**, 1142–1155, 2014.

We present a novel partner-specific protein–protein interaction site prediction method called PAIRpred. Unlike most existing machine learning binding site prediction methods, PAIRpred uses information from *both* proteins in a protein complex to predict pairs of interacting residues from the two proteins. PAIRpred captures sequence and structure information about residue pairs through pairwise kernels that are used for training a support vector machine classifier. As a result, PAIRpred presents a more detailed model of protein binding, and offers state of the art accuracy in predicting binding sites at the protein level as well as inter-protein residue contacts at the complex level.

The READY program: Building a global potential energy surface and reactive dynamic simulations for the hydrogen combustion

César Mogo [Centro de Investigação em Química do Algarve Universidade do Algarve], João Brandão

J. Comp. Chem., **35**, 1330–1337, 2014.

READY (REActive DYnamics) is a program for studying reactive dynamic systems using a global potential energy surface (PES) built from previously existing PESs corresponding to each of the most important elementary reactions present in the system. We present an application to the combustion dynamics of a mixture of hydrogen and oxygen using accurate PESs for all the systems involving up to four oxygen and hydrogen atoms.

Protein Secondary Structure

Probing Sequence Dependence of Folding Pathway of α -Helix Bundle Proteins through Free Energy Landscape Analysis

Qiang Shao [Chinese Academy of Sciences]

J. Phys. Chem. B., **118**, 5891–5900, 2014.

A comparative study on the folding of multiple three- α -helix bundle proteins including α 3D, α 3W, and the B domain of protein A (BdpA) is presented. The use of integrated-tempering-sampling molecular dynamics simulations achieves reversible folding and unfolding events in individual short trajectories, which thus provides an efficient approach to sufficiently sample the configuration space of protein and delineate the folding pathway of α -helix bundle. The detailed free energy landscape analyses indicate that the folding mechanism of α -helix bundle is not uniform but sequence dependent.

Protein Conformational Analysis

Packing interface energetics in different crystal forms of the λ Cro dimer

Logan S. Ahlstrom , Osamu Miyashita [RIKEN Advanced Institute for Computational Science

Proteins: Stru. Fun. & Bioinf., **82**, 1128–1141, 2014.

Variation among crystal structures of the λ Cro dimer highlights conformational flexibility. The structures range from a wild type closed to a mutant fully open conformation, but it is unclear if each represents a stable solution state or if one may be the result of crystal packing. Here we use molecular dynamics (MD) simulation to investigate the energetics of crystal packing interfaces and the influence of site-directed mutagenesis on them in order to examine the effect of crystal packing on wild type and mutant Cro dimer conformation.

Performance of four different force fields for simulations of dipeptide conformations: GlyGly, GlyGly⁻, GlyGly · Cl⁻, GlyGly · Na⁺ and GlyGly · (H₂O)₂

Chen Dong, Li Yong-Zhi, Wei Zhi-Chao, Liu Bo [Henan University]

J. Mol.Mod., **20**, 2279, 2014.

Monte-Carlo conformational searches with four kinds of force fields (AMBER94, MM3*, MMFFs, and OPLS-2005) were performed on glycylglycine (GlyGly), deprotonated glycylglycine (GlyGly⁻), glycylglycine chloride anion complex (GlyGly · Cl⁻), glycylglycine sodium cation complex (GlyGly · Na⁺) and glycylglycine dihydrate [GlyGly · (H₂O)₂]. Combined with Hartree-Fock (HF) and second-order Møller-Plesset (MP2) optimizations, conformations within an energy of 20 kJ mol⁻¹ were predicted. After MP2 calculations, the geometries and relative energies of the predicted structures were the same regardless of the force field used.

Computational Screening and Selection of Cyclic Peptide Hairpin Mimetics by Molecular Simulation and Kinetic Network Models

Asghar M. Razavi, William M. Wuest, Vincent A. Voelz [Temple University,]

J.Chem. Infor. and Mod. **54**, 1425–1432, 2014.

Designing peptidomimetic compounds to have a preorganized structure in solution is highly nontrivial. To show how simulation-based approaches can help speed this process, we performed an extensive simulation study of designed cyclic peptide mimics of a β -hairpin from bacterial protein LapD involved in a protein–protein interaction (PPI) pertinent to bacterial biofilm formation. We used replica exchange molecular dynamics (REMD) simulation to screen 20 covalently cross-linked designs with varying stereochemistry and selected the most favorable of these for massively parallel simulation on Folding@home in explicit solvent.

Protein Structure Analysis

An efficient parallel algorithm for accelerating computational protein design

Yichao Zhou, Wei Xu, Bruce R. Donald, Jianyang Zeng[Tsinghua University]

Bioinformatics. **30**, i255-i263, 2014.

In this article, we improve the efficiency of computing A* heuristic functions for protein design and propose a variant of A* algorithm in which the search process can be performed on a single GPU in a massively parallel fashion. In addition, we make some efforts to address the memory exceeding problem in A* search. As a result, our enhancements can achieve a significant speedup of the A*-based protein design algorithm by four orders of magnitude on large-scale test data through pre-computation and parallelization, while still maintaining an acceptable memory overhead.

Insilico modeling and molecular dynamic simulation of claudin-1 point mutations in HCV infection

Bhavaniprasad Vipperla, J. Febin Prabhu Dass, S. Jayanthi[VIT University]

J. Biomol. Stru. and Dyn., **32**, 1443-1455, 2014.

Claudin-1 (CLDN1) in association with envelope glycoprotein (CD81) mediates the fusion of HCV into the cytosol. Recent studies have indicated that point mutations in CLDN1 are important for the entry of hepatitis C virus (HCV). To validate these findings, we employed a computational platform to investigate the structural effect of two point mutations (I32M and E48K). Initially, three-dimensional co-ordinates for CLDN1 receptor sequence were generated. Then, three mutant models were built using the point mutation including a double mutant (I32M/E48K) model from the native model structure.

Mechanistic details for anthraniloyl transfer in PqsD: the initial step in HHQ biosynthesis

Michael C. Hutter[Saarland University], Christian Brengel, Matthias Negri, Claudia Henn, Christina Zimmer, Rolf W. Hartmann, Martin Empting, Anke Steinbach

J. Mol.Mod., **20**, 2255, 2014.

PqsD mediates the conversion of anthraniloyl-coenzyme A (ACoA) to 2-heptyl-4-hydroxyquinoline (HHQ), a precursor of the *Pseudomonas* quinolone signal (PQS) molecule. Here, we used molecular dynamics simulations to obtain the structural position of the substrate ACoA in the binding pocket of PqsD, and semiempirical molecular orbital calculations to study the reaction mechanism for the catalytic cleavage of ACoA. Our findings suggest a nucleophilic attack of the deprotonated sulfur of Cys112 at the carbonyl carbon of ACoA and a switch in the protonation pattern of His257 whereby N_δ is protonated and the proton of N_ε is shifted to the sulfur of CoA during the reaction.

Protein Dynamics

Combination of Genetic Screening and Molecular Dynamics as a Useful Tool for Identification of Disease-Related Mutations: ZASP PDZ Domain G54S Mutation Case

Filip Fratev[Bulgarian Academy of Sciences], Elina Mihaylova, Ilza Pajeva

J.Chem. Infor. and Mod. **54**, 1524–1536, 2014.

Cypher/ZASP (LDB3 gene) is known to interact with a network of proteins. It binds to α -actinin and the calcium voltage channels (LTCC) via its PDZ domain. Here we report the identification of a highly conserved ZASP G54S mutation classified as a variant of unknown significance in a sample of an adult with hypertrophic cardiomyopathy (HCM). The initial bioinformatics calculations strongly evaluated G54S as damaging. Furthermore, we employed accelerated and classical molecular dynamics and free energy calculations to study the structural impact of this mutation on the ZASP apo form and to address the question of whether it can be linked to HCM.

Rapid Sampling of Folding Equilibria of β -Peptides in Methanol Using a Supramolecular Solvent Model

Wei Huang, Sereina Riniker, Wilfred F. van Gunsteren [Swiss Federal Institute of Technology]

J. Chem. Theor. and Comp. **10**, 2213–2223, 2014.

Molecular dynamics simulation of biomolecules in solvent using an atomic model for both the biomolecules and the solvent molecules is still computationally rather demanding considering the time scale of the biomolecular motions. The use of a supramolecular coarse-grained (CG) model can speed up the simulation considerably, but it also reduces the accuracy inevitably. Here, a previously published CG methanol model is reparametrized, and then a 1:1 mixture of FG and CG methanol is used to calibrate the FG-CG interactions using thermodynamic and dielectric screening data for liquid methanol.

Resolution-Adapted All-Atomic and Coarse-Grained Model for Biomolecular Simulations

Lin Shen , Hao Hu [The University of Hong Kong-Shenzhen Institute of Research and Innovation]

J. Chem. Theor. and Comp. **10**, 2528–2536, 2014.

We develop here an adaptive multiresolution method for the simulation of complex heterogeneous systems such as the protein molecules. The target molecular system is described with the atomistic structure while maintaining concurrently a mapping to the coarse-grained models. The theoretical model, or force field, used to describe the interactions between two sites is automatically adjusted in the simulation processes according to the interaction distance/strength.

Unfolding of beta-lactoglobulin on the surface of polystyrene nanoparticles: Experimental and computational approaches

Matteo Miriani, Ivano Eberini, Stefania Iametti, Pasquale Ferranti, Cristina Sensi Francesco Bonomi [University of Milan]

Proteins: Stru. Fun. & Bioinf. **82**, 1272–1282, 2014.

Structural changes ensuing from the non-covalent absorption of bovine beta-lactoglobulin (BLG) on the surface of polystyrene nanoparticles were investigated by using spectroscopic approaches, by assessing the reactivity of specific residues, and by limited proteolysis/mass spectrometry. Also, the immunoreactivity of absorbed and free BLG was compared. All these approaches indicated substantial rearrangements of the protein structure in the absorbed state, in spite of the reported structural rigidity of BLG. Changes made evident by experimental measurements were confirmed by computational approaches.

Protein Dynamics (Cont'd)

Constant pH molecular dynamics of proteins in explicit solvent with proton tautomerism

Garrett B. Goh, Benjamin S. Hulbert, Huiqing Zhou , Charles L. Brooks III [930 N. University]

Proteins: Stru. Fun. & Bioinf., **82**, 1319–1331, 2014.

pH is a ubiquitous regulator of biological activity, including protein-folding, protein-protein interactions, and enzymatic activity. Existing constant pH molecular dynamics (CPHMD) models that were developed to address questions related to the pH-dependent properties of proteins are largely based on implicit solvent models. We report on an explicit solvent constant pH molecular dynamics framework based on multi-site λ -dynamics (CPHMD^{MS λ D}). In the CPHMD^{MS λ D} framework, we performed seamless alchemical transitions between protonation and tautomeric states using multi-site λ -dynamics, and designed novel biasing potentials to ensure that the physical end-states are predominantly sampled.

All-atom and coarse-grained simulations of the forced unfolding pathways of the SNARE complex

Wenjun Zheng [University at Buffalo]

Proteins: Stru. Fun. & Bioinf., **82**, 1376–1386, 2014.

The SNARE complex, consisting of three proteins (VAMP2, syntaxin, and SNAP-25), is thought to drive membrane fusion by assembling into a four-helix bundle through a zippering process. In support of the above zippering model, a recent single-molecule optical tweezers experiment by Gao *et al.* revealed a sequential unzipping of SNARE along VAMP2 in the order of the linker domain $\rightarrow$ the C-terminal domain $\rightarrow$ the N-terminal domain. To offer detailed structural insights to this unzipping process, we have performed all-atom and coarse-grained steered molecular dynamics (sMD) simulations of the forced unfolding pathways of SNARE using different models and force fields.

Efficient 3D kinetic monte carlo method for modeling of molecular structure and dynamics

Mikhail Panshenskov, Ilia A. Solov'yov [University of Southern Denmark] , Andrey V. Solov'yov

J. Comp. Chem., **35**, 1317–1329, 2014.

Self-assembly of molecular systems is an important and general problem that intertwines physics, chemistry, biology, and material sciences. Through understanding of the physical principles of self-organization, it often becomes feasible to control the process and to obtain complex structures with tailored properties, for example, bacteria colonies of cells or nanodevices with desired properties. Theoretical studies and simulations provide an important tool for unraveling the principles of self-organization and, therefore, have recently gained an increasing interest.

Free Energy Calculations

Role of Deprotonation Free Energies in pKa Prediction and Molecule Ranking

M. S. Bodnarchuk[Imperial College London], D. M. Heyes, D. Dini, S. Chahine, S. Edwards

J. Chem. Theor. and Comp., **10**, 2537–2545, 2014.

A computationally efficient classical molecular simulation technique is derived for ranking the pKa values of a set of chemically similar congeneric molecules in an implicit solvent model of water. This uses the deprotonation free energy of the titratable group in the gas and aqueous phases obtained by thermodynamic integration (TI). For a series of alcohols and acids a strong linear correlation is demonstrated between the experimental pKa and the deprotonation free energy difference in the gas and liquid phases

Ligand Binding/Docking

Replica-Exchange Molecular Dynamics Simulation of Basic Fibroblast Growth Factor Adsorption on Hydroxyapatite

Chenyi Liao , Jian Zhou [South China University of Technology]

J. Phys. Chem. B., **118**, 5843–5852, 2014.

The adsorption of basic fibroblast growth factor (bFGF) on the hydroxyapatite (001) surface was investigated by a combination of replica-exchange molecular dynamics (REMD) and conventional molecular dynamics (CMD) methods. In CMD, the protein cannot readily cross the surface water layer, whereas in REMD, the protein can cross the adsorption barrier from the surface water layer and go through weak, medium, then strong adsorption states with three energetically preferred configurations: heparin-binding-up (HP-up), heparin-binding-middle (HP-middle), and heparin-binding-down (HP-down).

Enzyme Catalysis

Evidence for the Role of Active Site Residues in the Hairpin Ribozyme from Molecular Simulations along the Reaction Path

Hugh Heldenbrand, Pawel A. Janowski, George Giambaşu, Timothy J. Giese, Joseph E. Wedekind, Darrin M. York [Rutgers University]

J. Am. Chem. Soc., 2013, **136**, 7789–7792, 2014.

The hairpin ribozyme accelerates a phosphoryl transfer reaction without catalytic participation of divalent metal ions. Residues A38 and G8 have been implicated as playing roles in general acid and base catalysis, respectively. Here we explore the structure and dynamics of key active site residues using more than 1 μ s of molecular dynamics simulations of the hairpin ribozyme at different stages along the catalytic pathway.

Enzyme Catalysis (Cont'd)

The inhibitory effect of helenalin on telomerase activity is attributed to the alkylation of the CYS445 residue: Evidence from QM/MM simulations

Zhiqiang Zhang [Zhengzhou University of Light Industry],
Liancai Xu, Hon-Yeung Cheung

J. Mol. Graph. and Mod., **51**, 97-103, 2014.

Enhanced telomerase activity is a hallmark in the majority of cancer cells. Thus, understanding the interactions between telomerase and its inhibitors is fundamentally important for the development of novel anticancer drugs without severe side effects. In this study, the covalent binding of helenalin to CYS445 of telomerase (PDB ID: 3DU6) was simulated using combined quantum chemical and molecular mechanical (QM/MM) methods.

A QM/MM study of the catalytic mechanism of aspartate ammonia lyase

Jing Zhang, Yongjun Liu [Shandong University]

J. Mol. Graph. and Mod., **51**, 113-119, 2014.

Aspartate ammonia lyase (Asp) is one of three types of ammonia lyases specific for aspartate or its derivatives as substrates, which catalyzes the reversible reaction of L-aspartate to yield fumarate and ammonia. In this paper, the catalytic mechanism of Asp has been studied by using combined quantum-mechanical/molecular-mechanical (QM/MM) approach. The calculation results indicate that the overall reaction only contains two elementary steps.

Key Amino Acid Associated with Acephate Detoxification by *Cydia pomonella* Carboxylesterase Based on Molecular Dynamics with Alanine Scanning and Site-Directed Mutagenesis

Xue Qing Yang, Ji Yuan Liu, Xian Chun Li, Mao Hua Chen,
Ya Lin Zhang [Northwest A & F University]

J. Chem. Infor. and Mod. **54**, 1356–1370, 2014.

Insecticide-detoxifying carboxylesterase (CE) gene CpCE-1 was cloned from *Cydia pomonella*. Molecular dynamics (MD) simulation and computational alanine scanning (CAS) indicate that Asn 232 in CpCE-1 constitutes an approximate binding hot-spot with a binding free energy difference ($\Delta\Delta G_{\text{bind}}$) value of 3.66 kcal/mol. The catalytic efficiency (kcat/km) of N232A declined dramatically, and the half inhibitory concentrations (IC50) value increased by more than 230-fold. Metabolism assay in vitro reveals that the acephate could be metabolized by wild CpCE-1, whereas N232A mutation is unable to metabolize the acephate, which suggests that the hot-spot Asn 232 is a crucial residue for acephate metabolism.

Molecular Dynamics Simulations Reveal a Novel Mechanism for ATP Inhibition of Insulin Degrading Enzyme

Carlos H. B. da Cruz , Gustavo Seabra [Cidade Universitária,]

J. Chem. Infor. and Mod. **54**, 1380–1390, 2014.

Regulation of brain levels of the Amyloid- β 42 (A β 42) polypeptide by IDE has recently been linked with possible routes for new therapies against Alzheimer's disease (AD). One important aspect is the regulatory mechanism of IDE by ATP, which is an IDE activator in degrading small peptides and an inhibitor in degrading larger peptides, such as A β 42. This relationship was investigated in this study. We present molecular dynamics simulations of A β 42 complexed with IDE, in the absence or presence of either ATP or excess Na⁺ and Cl⁻ ions.

Enzyme Catalysis (Cont'd)

Computational Analysis of Negative and Positive Allosteric Modulator Binding and Function in Metabotropic Glutamate Receptor 5 (In)Activation

James A. R. Dalton, Xavier Gómez-Santacana, Amadeu Llebaria, and Jesús Giraldo [Universitat Autònoma de Barcelona]

J.Chem. Infor. and Mod. **54**, 1476–1487, 2014.

Metabotropic glutamate receptors (mGluRs) are high-profile G-protein coupled receptors drug targets because of their involvement in several neurological disease states, and mGluR5 in particular is a subtype whose controlled allosteric modulation, both positive and negative, can potentially be useful for the treatment of schizophrenia and relief of chronic pain, respectively. Here we model mGluR5 with a collection of positive and negative allosteric modulators (PAMs and NAMs) in both active and inactive receptor states, in a manner that is consistent with experimental information, using a specialized protocol that includes homology to increase docking accuracy, and receptor relaxation to generate an individual induced fit with each allosteric modulator.

Structural and functional analysis of a novel psychrophilic β -mannanase from *Glaciozyma antarctica* PI12

Sepideh Parvizpour, Jafar Razmara, Aizi Nor Mazila Ramli, Rosli Md Illias, Mohd Shahir Shamsir [Universiti Teknologi Malaysia]

J. Comp. Aided. Mol. Design, **28**, 685-698, 2014.

The structure of a novel psychrophilic β -mannanase enzyme from *Glaciozyma antarctica* PI12 yeast has been modelled and analysed in detail. To our knowledge, this is the first attempt to model a psychrophilic β -mannanase from yeast. To this end, a 3D structure of the enzyme was first predicted using a threading method because of the low sequence identity (<30 %) using MODELLER9v12 and simulated using GROMACS at varying low temperatures for structure refinement.

Molecular Dynamics Simulation of Nitrobenzene Dioxygenase Using AMBER Force Field

Anna Pabis, Inacrist Geronimo, Darrin M. York, Piotr Paneth [University of Technology]

J. Chem. Theor. and Comp, **10**, 2246–2254, 2014.

Molecular dynamics simulation of the oxygenase component of nitrobenzene dioxygenase (NBDO) system, a member of the naphthalene family of Rieske nonheme iron dioxygenases, has been carried out using the AMBER force field combined with a new set of parameters for the description of the mononuclear nonheme iron center and iron-sulfur Rieske cluster. Simulation results provide information on the structure and dynamics of nitrobenzene dioxygenase in an aqueous environment and shed light on specific interactions that occur in its catalytic center.

Interaction of β -cyclodextrin as catalyst with acetophenone in asymmetric reaction: a theoretical survey

Yali Wan, Xueye Wang [Xiangtan University], Na Liu

J. Mol.Mod., **20**, 2268, 2014.

The asymmetric reduction of acetophenone with sodium borohydride in the presence of β -cyclodextrin (β -CD) as catalyst can improve selectivity and yield. The interaction between acetophenone and β -CD plays an important role for the reduction of acetophenone. This work studies the reaction of acetophenone in the presence of β -CD using density functional theory (DFT) method. Energy is investigated to find out the lowest energy of two possible complexation models. The geometrical structure confirms that acetophenone inserts into the cavity mainly from the secondary hydroxyl side.

Protein-Protein Interactions

ZDOCK server: interactive docking prediction of protein–protein complexes and symmetric multimers

Brian G. Pierce, Kevin Wiehe, Howook Hwang, Bong-Hyun Kim, Thom Vreven, Zhiping Weng[Boston University]

Bioinformatics. **30**, 1771–1773, 2014.

We present a user-friendly protein docking server, based on the rigid-body docking programs ZDOCK and M-ZDOCK, to predict structures of protein–protein complexes and symmetric multimers. With a goal of providing an accessible and intuitive interface, we provide options for users to guide the scoring and the selection of output models, in addition to dynamic visualization of input structures and output docking models.

Rational Design of Topographical Helix Mimics as Potent Inhibitors of Protein–Protein Interactions

Brooke Bullock Lao, Kevin Drew, Danielle A. Guarracino, Thomas F. Brewer, Daniel W. Heindel, Richard Bonneau [New York University], Paramjit S. Arora

J. Am. Chem. Soc., 2013, **136**, 7877–7888 , 2014.

Protein–protein interactions encompass large surface areas, but often a handful of key residues dominate the binding energy landscape. Rationally designed small molecule scaffolds that reproduce the relative positioning and disposition of important binding residues, termed “hotspot residues”, have been shown to successfully inhibit specific protein complexes. Although this strategy has led to development of novel synthetic inhibitors of protein complexes, often direct mimicry of natural amino acid residues does not lead to potent inhibitors.

Computational Method To Identify Druggable Binding Sites That Target Protein–Protein Interactions

Hubert Li, Vinod Kasam, Christofer S. Tautermann, Daniel Seeliger, Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J.Chem. Infor. and Mod. **54**, 1391–1400, 2014.

Protein–protein interactions are implicated in the pathogenesis of many diseases and are therefore attractive but challenging targets for drug design. One of the challenges in development is the identification of potential druggable binding sites in protein interacting interfaces. Identification of interface surfaces can greatly aid rational drug design of small molecules inhibiting protein–protein interactions. In this work, starting from the structure of a free monomer, we have developed a ligand docking based method, called “FindBindSite” (FBS), to locate protein–protein interacting interface regions and potential druggable sites in this interface.

A functional feature analysis on diverse protein–protein interactions: application for the prediction of binding affinity

Jiesi Luo, Yanzhi Guo, Yun Zhong, Duo Ma, Wenling Li, Menglong Li[Sichuan University]

J. Comp. Aided. Mol. Design, **28**, 619–629, 2014.

Protein–protein interactions (PPIs) play crucial roles in diverse cellular processes. There are different types of PPIs based on the composition, affinity and whether the association is permanent or transient. Analyzing the diversity of PPIs at the atomic level is crucial for uncovering the key features governing the interactions involved in PPI. A systematic physico-chemical and conformational studies were implemented on interfaces involved in different PPIs, including crystal packing, weak transient heterodimers, weak transient homodimers, strong transient heterodimers and homodimers.

Protein Protein Interactions (Cont'd)

Benchmarking protein–protein interface predictions: Why you should care about protein size

Juliette Martin [Université Lyon 1]

Proteins: Stru. Fun. & Bioinf., **82**, 1444–1452, 2014.

A number of predictive methods have been developed to predict protein–protein binding sites. Each new method is traditionally benchmarked using sets of protein structures of various sizes, and global statistics are used to assess the quality of the prediction. We investigate the bias due to the size effect when benchmarking protein-protein interface prediction on the widely used docking benchmark 4.0. First, we simulate random scores that favor small proteins over large ones. Instead of the 0.5 AUC (Area Under the Curve) value expected by chance, these biased scores result in an AUC equal to 0.6 using hypergeometric distributions, and up to 0.65 using constant scores.

Membrane Proteins and Lipid Peptide Interactions

Using thermodynamic integration MD simulation to compute relative protein–ligand binding free energy of a GSK3 β kinase inhibitor and its analogs

Hsing-Chou Lee, Wen-Chi Hsu, An-Lun Liu, Chia-Jen Hsu, Ying-Chieh Sun [National Taiwan Normal University]

J. Mol.Graph. and Mod., **51**, 37-49, 2014.

Thermodynamic integration molecular dynamics simulation was used to investigate how TI-MD simulation preforms in reproducing relative protein–ligand binding free energy of a pair of analogous GSK3 β kinase inhibitors of available experimental data (see Fig. 1), and to predict the affinity for other analogs. The computation for the pair gave a $\Delta\Delta G$ of 1.0 kcal/mol, which was in reasonably good agreement with the experimental value of -0.1 kcal/mol. The error bar was estimated at 0.5 kcal/mol. Subsequently, we employed the same protocol to proceed with simulations to find analogous inhibitors with a stronger affinity.

Systematic implicit solvent coarse graining of dimyristoylphosphatidylcholine lipids

Alexander Mirzoev [Stockholm University] , Alexander P. Lyubartsev

J. Comp. Chem., **35**, 1208–1218, 2014.

We have used systematic structure-based coarse graining to derive effective site–site potentials for a 10-site coarse-grained dimyristoylphosphatidylcholine (DMPC) lipid model and investigated their state point dependence. The potentials provide for the coarse-grained model the same site–site radial distribution functions, bond and angle distributions as those computed in atomistic simulations carried out at four different lipid–water molar ratios. It was shown that there is a non-negligible dependence of the effective potentials on the concentration at which they were generated, which is also manifested in the properties of the lipid bilayers simulated using these potentials.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

DFT and MD study of the divalent-cation-mediated interaction of ochratoxin A with DNA nucleosides

Jozef Motyčka, Pavel Mach[Comenius University in Bratislava], Milan Melicherčík, Jan Urban

J. Mol.Mod., **20**, 2274, 2014.

Aptamers are ligand-binding nucleic acids with affinities and selectivities that make them useful for the detection of a variety of compounds, including ochratoxin A. Theoretical methods can be applied to study the recognition interaction between aptamers and the ochratoxin A molecule. In this work, molecular dynamics simulations and quantum chemical calculations performed at the DFT level of theory were used to study the structures and energies of aptamers and aptamer–ochratoxin A complexes.

Universal Method for Embedding Proteins into Complex Lipid Bilayers for Molecular Dynamics Simulations

Matti Javanainen [Tampere University of Technology]

J. Chem. Theor. and Comp., **10**, 2577–2582, 2014.

The growing interest toward membrane protein simulations calls for a universal and efficient protocol for embedding multiple proteins simultaneously into asymmetric many-component lipid membranes. To this end, here, we present a new and simple technique based on pushing proteins into a lipid membrane from its side by applying a high lateral pressure on the system. This approach is compatible with most (if not all) simulation software packages, and it is independent of external program codes.

Aromatic Interactions Modulate the 5'-Base Selectivity of the DNA-Binding Autoantibody ED-10

Yi An, Rajesh K. Raju, Tongxiang Lu, Steven E. Wheeler [Texas A&M University]

J. Phys. Chem. B., **118**, 5653–5659, 2014.

We present detailed computational analyses of the binding of four dinucleotides to a highly sequence-selective single-stranded DNA (ssDNA) binding antibody (ED-10) and selected point mutants. Anti-DNA antibodies are central to the pathogenesis of systemic lupus erythematosus (SLE), and a more complete understanding of the mode of binding of DNA and other ligands will be necessary to elucidate the role of anti-DNA antibodies in the kidney inflammation associated with SLE. Classical molecular mechanics based molecular dynamics simulations and density functional theory (DFT) computations were applied to pinpoint the origin of selectivity for the 5'-nucleotide.

Molecular Structures of C- and N-Terminus Cysteine Modified Cecropin P1 Chemically Immobilized onto Maleimide-Terminated Self-Assembled Monolayers Investigated by Molecular Dynamics Simulation

Zunliang Wang, Xiaofeng Han, Nongyue He, Zhan Chen, Charles L. Brooks, III [University of Michigan]

J. Phys. Chem. B., **118**, 5670–5680, 2014.

Biosensors using peptides or proteins chemically immobilized on surfaces have many advantages such as better sensitivity, improved stability, and longer shelf life compared to those prepared using physically adsorbed biomolecules. Chemical immobilization can better control the interfacial conformation and orientation of peptides and proteins, leading to better activity of these biomolecules. In this research, molecular dynamics (MD) simulations were employed to systematically investigate the structure and dynamics of surface-tethered antimicrobial peptide cecropin P1 (CP1) modified with a cysteine residue at the C- (CP1c) or N-terminus (cCP1).

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Water and Membrane Dynamics in Suspensions of Lipid Vesicles Functionalized with Poly(ethylene glycol)s

Eduardo M. Clop, Ana K. Chattah, María A. Perillo
[Universidad Nacional de Córdoba]

J. Phys. Chem. B., **118**, 6150–6158, 2014.

The present work was aimed at studying the molecular dynamics at different levels of model membranes having a simulated glycolix, with focus on the molecular crowding conditions at the lipid–water interfacial region. Thus, binary mixtures of dipalmitoylphosphatidylcholine (dpPC) and a poly(ethylene glycol) (PEGn) derivative of dipalmitoylphosphatidylethanolamine (PE) (where $n = 350, 1000, \text{ and } 5000$, respectively, refer to PEG molecular masses) were submitted to ^1H spin–lattice relaxation time (T_1) and ^{31}P NMR spectra analysis.

Atomistic mechanisms of huntingtin N-terminal fragment insertion on a phospholipid bilayer revealed by molecular dynamics simulations

Sébastien Côté, Guanghong Wei, Normand Mousseau
[Université de Montréal]

Proteins: Stru. Fun. & Bioinf., **82**, 1409–1427, 2014.

The huntingtin protein is characterized by a segment of consecutive glutamines (Q_N) that is responsible for its fibrillation. As with other amyloid proteins, misfolding of huntingtin is related to Huntington's disease through pathways that can involve interactions with phospholipid membranes. Experimental results suggest that the N-terminal 17-amino-acid sequence (htt^{NT}) positioned just before the Q_N region is important for the binding of huntingtin to membranes. Through all-atom explicit solvent molecular dynamics simulations, we unveil the structure and dynamics of the $\text{htt}^{\text{NT}}Q_N$ fragment on a phospholipid membrane at the atomic level.

Protein Folding

REMD and umbrella sampling simulations to probe the energy barrier of the folding pathways of engrailed homeodomain

Vinod Jani, Uddhaves B. Sonavane, Rajendra Joshi [Pune University Campus Ganeshkhind]

J. Mol.Mod., **20**, 2283, 2014.

Proteins fold by diverse pathways which depend on the energy barriers involved in reaching different intermediates. There has been a lot of development in the theoretical aspects of protein folding, from force-field to simulation techniques. One such simulation approach is replica exchange molecular dynamics simulation (REMD), which provides an efficient conformational sampling method to understand the events involved in protein folding. In this study, an attempt is made to explore the folding funnel of engrailed homeodomain protein (EnHD) using REMD simulations.

Mechanism of Folding and Binding of an Intrinsically Disordered Protein As Revealed by ab Initio Simulations

Mateusz Kurcinski, Andrzej Kolinski, Sebastian Kmiecik
[University of Warsaw]

J. Chem. Theor. and Comp., **10**, 2224–2231, 2014.

A complex of the phosphorylated kinase-inducible domain (pKID) with its interacting domain (KIX) is a model system for studies of mechanisms by which intrinsically unfolded proteins perform their functions. These mechanisms are not fully understood. Using an efficient coarse-grained model, ab initio simulations were performed of the coupled folding and binding of the pKID to the KIX. The simulations start from an unbound, randomly positioned and disordered pKID structure. During the simulations the pKID chain and its position remain completely unrestricted, while the KIX backbone is limited to near-native fluctuations.

Protein Folding (Cont'd)

Mechanism of the All- α to All- β Conformational Transition of RfaH-CTD: Molecular Dynamics Simulation and Markov State Model

Shanshan Li, Bing Xiong, Yuan Xu, Tao Lu, Xiaomin Luo, Cheng Luo, Jingkang Shen, Kaixian Chen, Mingyue Zheng [Chinese Academy of Sciences], Hualiang Jiang

J. Chem. Theor. and Comp., **10**, 2255–2264, 2014.

The C-terminal domain of the bacterial transcription antiterminator RfaH undergoes a dramatic all- α -helix to all- β -barrel transition when released from its N-terminal domain. These two distinct folding patterns correspond to different functions: the all- α state acts as an essential regulator of transcription to ensure RNA polymerase binding, whereas the all- β state operates as an activator of translation by interacting with the ribosomal protein S10 and recruits ribosomal mRNA. To understand the mechanism behind this extraordinary functionally relevant structural transition, we constructed Markov state models using an adaptive seeding method.

Role of Backbone Dipole Interactions in the Formation of Secondary and Supersecondary Structures of Proteins

Sai J. Ganesan, S. Matysiak [University of Maryland]

J. Chem. Theor. and Comp., **10**, 2569–2576, 2014.

We present a generic solvated coarse-grained protein model that can be used to characterize the driving forces behind protein folding. Each amino acid is coarse-grained with two beads, a backbone, and a side chain. Although the backbone beads are modeled as polar entities, side chains are hydrophobic, polar, or charged, thus allowing the exploration of how sequence patterning determines a protein fold. The change in orientation of the atoms of the coarse-grained unit is captured by the addition of two oppositely charged dummy particles inside the backbone coarse-grained bead.

Ab initio protein folding simulations using atomic burials as informational intermediates between sequence and structure

Marx Gomes van der Linden, Diogo César Ferreira, Leandro Cristante de Oliveira, José N. Onuchic, Antônio F. Pereira de Araújo [Universidade de Brasília]

Proteins: Stru. Fun. & Bioinf., **82**, 1186–1199, 2014.

The three-dimensional structure of proteins is determined by their linear amino acid sequences but decipherment of the underlying protein folding code has remained elusive. Recent studies have suggested that burials, as expressed by atomic distances to the molecular center, are sufficiently informative for structural determination while potentially obtainable from sequences. Here we provide direct evidence for this distinctive role of burials in the folding code, demonstrating that burial propensities estimated from local sequence can indeed be used to fold globular proteins in ab initio simulations.

Nucleic Acids

Unraveling the outcome of 16S rDNA-based taxonomy analysis through mock data and simulations

Ali May [University of Amsterdam and VU University Amsterdam], Sanne Abeln, Wim Crielaard, Jaap Heringa, Bernd W. Brandt

Bioinformatics. **30**, 1530-1538, 2014.

16S rDNA pyrosequencing is a powerful approach that requires extensive usage of computational methods for delineating microbial compositions. We use in silico microbial datasets to better understand how the experimental data are transformed into taxonomic clusters by computational methods. We were able to qualitatively replicate the raw experimental pyrosequencing data after rigorously adjusting existing simulation software. This allowed us to simulate datasets of real-life complexity, which we used to assess the influence and performance of two widely used pre-processing methods along with 11 clustering algorithms.

Nucleic Acids (Cont'd)

Deamination features of 5-hydroxymethylcytosine, a radical and enzymatic DNA oxidation product

André Grand, Nelly Jorge, Christophe Morell, Jean Cadet, Leif A. Eriksson [University of Gothenburg]

J. Mol.Mod., **20**, 2290, 2014.

The 5-methylcytosine derivative 5-hydroxymethylcytosine (5hmCyt), which is generated via enzymatic oxidation, is sometimes referred to as the sixth nucleobase due to its widespread presence in the DNA of brain and embryonic stem cells. In this study, we used density functional based methods and reactivity indices from conceptual DFT to explore the mechanism and key features of the hydrolytic deamination of 5hmCyt. The data obtained are used to compare and contrast this deamination reaction with those of other cytosine derivatives.

Atomistic Investigation of the Effect of Incremental Modification of Deoxyribose Sugars by Locked Nucleic Acid (β -d-LNA and α -l-LNA) Moieties on the Structures and Thermodynamics of DNA–RNA Hybrid Duplexes

Gorle Suresh , U. Deva Priyakumar [International Institute of Information Technology]

J. Phys. Chem. B., **118**, 5853–5863, 2014.

Chemically modified oligonucleotides offer many possibilities in utilizing their special features for a vast number of applications in nucleic acid based therapies and synthetic molecular biology. Locked nucleic acid analogues (α -/ β -LNA) are modifications having an extra ring of 2'-O,4'-C-methylene group in the furanose sugar. LNA strands have been shown to exhibit high binding affinity toward RNA and DNA strands, and the resultant duplexes show significantly high melting temperatures. In the present study, molecular dynamics (MD) simulations were performed on DNA–RNA hybrid duplexes by systematically modifying their deoxyribose sugars with locked nucleic acid analogues.

All-atom polarizable force field for DNA based on the classical drude oscillator model

Alexey Savelyev , Alexander D. MacKerell Jr.[University of Maryland,]

J. Comp. Chem., **35**, 1219–1239, 2014.

Presented is a first generation atomistic force field (FF) for DNA in which electronic polarization is modeled based on the classical Drude oscillator formalism. The DNA model is based on parameters for small molecules representative of nucleic acids, including alkanes, ethers, dimethylphosphate, and the nucleic acid bases and empirical adjustment of key dihedral parameters associated with the phosphodiester backbone, glycosidic linkages, and sugar moiety of DNA. Our optimization strategy is based on achieving a compromise between satisfying the properties of the underlying model compounds in the gas phase targeting quantum mechanical (QM) data and reproducing a number of experimental properties of DNA duplexes in the condensed phase.

Surfaces, Catalysts, and Materials Subjects

Molecular dynamics study of the adsorption of anionic surfactant in a nonionic polymer brush

Hua Wang, Heng Zhang, Shiling Yuan, Chengbu Liu, Zhen Xu [Qilu University of Technology]

J. Mol.Mod., **20**, 2267, 2014.

The adsorption of the anionic surfactant, sodium dodecylsulfate (SDS) in poly(ethylene oxide) (PEO) brush was studied by molecular dynamics simulations. Our simulations revealed that surfactant can adsorb in polymer brush as micellar aggregates and the polymer would reside at the hydrocarbon-water interface of SDS micelles. This association between surfactant and polymer was mainly driven by the hydrophobic interaction between the polymer and surfactant tails.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Group-based QSAR and molecular dynamics mechanistic analysis revealing the mode of action of novel piperidinone derived protein-protein inhibitors of p53-MDM2

Sukriti Goyal, Sonam Grover, Jaspreet KaurDhanjal, Chetna Tyagi, Manisha Goyal, Abhinav Grover [Banasthali University]

J. Mol.Graph. and Mod., **51**, 64-72 , 2014.

Tumour suppressor p53 is known to play a central role in prevention of tumour development, DNA repair, senescence and apoptosis which is in normal cells maintained by negative feedback regulator MDM2 (Murine Double Minute 2). In case of dysfunctioning of this regulatory loop, tumour development starts thus resulting in cancerous condition. Inhibition of p53-MDM2 binding would result in activation of the tumour suppressor. In this study, a novel robust fragment-based QSAR model has been developed for piperidinone derived compounds experimentally known to inhibit p53-MDM2 interaction.

The use of docking-based comparative intermolecular contacts analysis to identify optimal docking conditions within glucokinase and to discover of new GK activators

Mutasem O. Taha[The University of Jordan], Maha Habash, Mohammad A. Khanfar

J. Comp. Aided. Mol. Design, **28**, 509-547, 2014.

Glucokinase (GK) is involved in normal glucose homeostasis and therefore it is a valid target for drug design and discovery efforts. GK activators (GKAs) have excellent potential as treatments of hyperglycemia and diabetes. The combined recent interest in GKAs, together with docking limitations and shortages of docking validation methods prompted us to use our new 3D-QSAR analysis, namely, docking-based comparative intermolecular contacts analysis (dbCICA), to validate docking configurations performed on a group of GKAs within GK binding site.

Quantitative Structure-Activity Relations (Cont'd)

Computational chemogenomics: Is it more than inductive transfer?

J. B. Brown, Yasushi Okuno, Gilles Marcou, Alexandre Varnek, Dragos Horvath[Univ. Strasbourg]

J. Comp. Aided. Mol. Design, **28**, 597-618, 2014.

High-throughput assays challenge us to extract knowledge from multi-ligand, multi-target activity data. In QSAR, weights are statically fitted to each ligand descriptor with respect to a single endpoint or target. However, computational chemogenomics (CG) has demonstrated benefits of learning from entire grids of data at once, rather than building target-specific QSARs. We explore the problem in the context of Support Vector Regression, using more than 9,400pK values of 31 GPCRs, where compound-protein interactions are represented by the concatenation of vectorial descriptions of compounds and proteins.

Potentials and Parameters

Adaptive Resolution Simulation of MARTINI Solvents

Julija Zavadlav, Manuel N. Melo, Ana V. Cunha, Alex H. de Vries, Siewert J. Marrink [University of Groningen], Matej Praprotnik

J. Chem. Theor. and Comp, **10**, 2591–2598, 2014.

We present adaptive resolution molecular dynamics simulations of aqueous and apolar solvents using coarse-grained molecular models that are compatible with the MARTINI force field. As representatives of both classes of solvents we have chosen liquid water and butane, respectively, at ambient temperature. The solvent molecules change their resolution back and forth between the atomistic and coarse-grained representations according to their positions in the system. The difficulties that arise from coupling to a coarse-grained model with a multimolecule mapping, for example, 4-to-1 mapping in the case of the Simple Point Charge (SPC) and MARTINI water models, could be successfully circumvented by using bundled water models.

Large-Scale Reactive Molecular Dynamics Simulation and Kinetic Modeling of High-Temperature Pyrolysis of the Gloeocapsomorpha prisca Microfossils

Chenyu Zou, Sumathy Raman[ExxonMobil Research and Engineering Co. (EMRE)], Adri C.T. van Duin

J. Phys. Chem. B., **118**, 6302–6315, 2014.

The ability to predict accurately the thermal conversion of complex carbonaceous materials is of value in both petroleum exploration and refining operations. Modeling the thermal cracking of kerogen under basinal heating conditions improves the predrill prediction of oil and gas yields and quality, thereby ultimately lowering the exploration risk. Reactive molecular dynamics (RMD) simulations were performed on systems consisting of 104 to 105 atoms at different densities and temperatures to derive the overall kinetic parameters and a lumped kinetic model for pyrolysis.

Potentials and Parameters (Cont'd)

An effective Coarse-grained model for biological simulations: Recent refinements and validations

Spyridon Vicatos, Anna Rychkova, Shayantani Mukherjee ,
Arieh Warshel[University of Southern California]

Proteins: Stru. Fun. & Bioinf., **82**, 1168–1185, 2014.

Exploring the free energy landscape of proteins and modeling the corresponding functional aspects presents a major challenge for computer simulation approaches. The use of various simplified CG models offers an effective way of sampling the landscape, but most current models are not expected to give a reliable description of protein stability and functional aspects. In this respect, our recent CG model offers significant advantage as it has been refined while focusing on its electrostatic free energy.

QM and QM/MM

Why the tautomerization of the G•C Watson–Crick base pair via the DPT does not cause point mutations during DNA replication? QM and QTAIM comprehensive analysis

Ol'ha O. Brovarets' , Dmytro M. Hovorun[National Academy
of Sciences of Ukraine]

J. Biomol. Stru. and Dyn., **32**, 1474-1499,2014.

The ground-state tautomerization of the G•C Watson–Crick base pair by the double proton transfer (DPT) was comprehensively studied in vacuo and in the continuum with a low dielectric constant ($\epsilon = 4$), corresponding to a hydrophobic interface of protein–nucleic acid interactions, using DFT and MP2 levels of quantum-mechanical (QM) theory and quantum theory “Atoms in molecules” (QTAIM). It was demonstrated using the conductor-like polarizable continuum model (CPCM) that the continuum with $\epsilon = 4$ does not qualitatively affect the course of the tautomerization reaction. The DPT in the G•C Watson–Crick base pair occurs without any intermediates both in vacuum and in the continuum with $\epsilon = 4$ at the DFT/MP2 levels of theory.

Exploring molecular structures, orbital interactions, intramolecular proton-transfer reaction kinetics, electronic transitions and complexation of 3-hydroxycoumarin species using DFT methods

Nuttawisit Yasarawan, Khajadpai Thipyapong [Burapha
University], Vithaya Ruangpornvisuti

J. Mol.Graph. and Mod., **51**, 13-26, 2014.

Optimal structures and electronic properties of various species of 3-hydroxycoumarin (3-HCou) have been explored using density functional theory (DFT) methods under polarizable continuum model (PCM) of solvation. Electron transfer from pyrone to benzene moieties is enhanced upon deprotonation. Anionic and radical species have similar orbital-interaction characteristics but the charges in the former are distributed more uniformly. The rate of intramolecular proton transfer for the neutral species increases many folds upon excitation.

Can Molecular Dynamics and QM/MM Solve the Penicillin Binding Protein Protonation Puzzle?

Jacqueline C. Hargis, Justin K. White, Yu Chen, H. Lee
Woodcock [University of South Florida,]

J.Chem. Infor. and Mod. **54**, 1412–1424, 2014.

Benzylpenicillin, a member of the β -lactam antibiotic class, has been widely used to combat bacterial infections since 1947. The general mechanism is well-known: a serine protease enzyme (i.e., DD-peptidase) forms a long lasting intermediate with the lactam ring of the antibiotic known as acylation, effectively preventing biosynthesis of the bacterial cell wall. Despite this overall mechanistic understanding, many details of binding and catalysis are unclear. Herein, a unique combination of MD simulations, QM/MM minimizations, and QM/MM orbital analyses is combined with systematic variation of active site residue protonation states.

QM and QM/MM (Cont'd)

QM Computations on Complete Nucleic Acids Building Blocks: Analysis of the Sarcin–Ricin RNA Motif Using DFT-D3, HF-3c, PM6-D3H, and MM Approaches

Holger Kruse, Marek Havrila, Jiří Šponer [CEITEC – Central European Institute of Technology]

J. Chem. Theor. and Comp., **10**, 2615–2629, 2014.

A set of conformations obtained from explicit solvent molecular dynamics (MD) simulations of the Sarcin–Ricin internal loop (SRL) RNA motif is investigated using quantum mechanical (QM, TPSS-D3/def2-TZVP DFT-D3) and molecular mechanics (MM, AMBER parm99bsc0+χol3 force field) methods. Solvent effects are approximated using implicit solvent methods (COSMO for DFT-D3; GB and PB for MM). Large-scale DFT-D3 optimizations of the full 11-nucleotide motif are compared to MM results and reveal a higher flexibility of DFT-D3 over the MM in the optimization procedure.

Cation– π interactions of methylated ammonium ions: A quantum mechanical study

Chaya Rapp [Yeshiva University], Elizabeth Goldberger, Nasim Tishbi, Rachel Kirshenbaum

Proteins: Stru. Fun. & Bioinf., **82**, 1494–1502, 2014.

Cation– π interactions of methylated ammonium ions play a key role in a broad range of biochemical systems. These include methyl-lysine binding proteins which bind to methylated sites on histone proteins, lysine demethylase enzymes which demethylate these sites, and neurotransmitter receptor complexes which bind choline-derived ligands. Recognition in these systems is achieved through an ‘aromatic cage’ motif in the binding site. Here we use high-level quantum mechanical calculations to address how cation– π interactions of methylated ammonium ions are modulated by a change in methylation state and interaction geometry.

Ab initio path-integral calculations of kinetic and equilibrium isotope effects on base-catalyzed RNA transphosphorylation models

Kin-Yiu Wong [Hong Kong Baptist University], Yuqing Xu and Darrin M. York

J. Comp. Chem., **35**, 1302–1316, 2014.

Detailed understandings of the reaction mechanisms of RNA catalysis in various environments can have profound importance for many applications, ranging from the design of new biotechnologies to the unraveling of the evolutionary origin of life. An integral step in the nucleolytic RNA catalysis is self-cleavage of RNA strands by 2'-O-transphosphorylation. Key to elucidating a reaction mechanism is determining the molecular structure and bonding characteristics of transition state. A direct and powerful probe of transition state is measuring isotope effects on biochemical reactions, particularly if we can reproduce isotope effect values from quantum calculations.

Comparative or Homology Modeling

Structures of TraI in solution

Nicholas J. Clark, Madushi Raththagala, Nathan T. Wright, Elizabeth A. Buenger, Joel F. Schildbach, Susan Krueger, Joseph E. Curtis [National Institute of Standards and Technology]

J. Mol.Mod., **20**, 2308, 2014.

Bacterial conjugation, a DNA transfer mechanism involving transport of one plasmid strand from donor to recipient, is driven by plasmid-encoded proteins. The F TraI protein nicks one F plasmid strand, separates cut and uncut strands, and pilots the cut strand through a secretion pore into the recipient. TraI is a modular protein with identifiable nickase, ssDNA-binding, helicase and protein-protein interaction domains. Here, we combine solution studies using small-angle scattering and circular dichroism spectroscopy with molecular Monte Carlo and molecular dynamics simulations to assess solution behavior of individual and groups of domains.

Toward an Optimal Docking and Free Energy Calculation Scheme in Ligand Design with Application to COX-1 Inhibitors

Yasmin Shamsudin Khan, Hugo Gutiérrez-de-Terán, Lars Boukharta, Johan Åqvist [Uppsala University]

J.Chem. Infor. and Mod. **54**, 1488–1499, 2014.

Cyclooxygenase-1 (COX-1) is one of the main targets of most pain-relieving pharmaceuticals. Although the enzyme is well characterized, it is known to be a difficult target for automated molecular docking and scoring. We collected from the literature a structurally diverse set of 45 nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2-selective inhibitors (coxibs) with a wide range of binding affinities for COX-1. The binding of this data set to a homology model of human COX-1 was analyzed with different combinations of molecular docking algorithms, scoring functions, and the linear interaction energy (LIE) method for estimating binding affinities.

Ligand Docking

Shuttle–Cargo Fusion Molecules of Transport Peptides and the hD2/3 Receptor Antagonist Fallypride: A Feasible Approach To Preserve Ligand–Receptor Binding?

Carmen Wängler [McGill University], Shafinaz Chowdhury, Georg Höfner, Petia Djurova, Enrico O. Purisima, Peter Bartenstein, Björn Wängler, Gert Fricker, Klaus T. Wanner, Ralf Schirrmacher

J.Med.Chem., **57**, 4368–4381, 2014.

To determine if the conjugation of a small receptor ligand to a peptidic carrier to potentially facilitate transport across the blood–brain barrier (BBB) by “molecular Trojan horse” transcytosis is feasible, we synthesized several transport peptide–fallypride fusion molecules as model systems and determined their binding affinities to the hD2 receptor. Although they were affected by conjugation, the binding affinities were found to be still in the nanomolar range (between 1.5 and 64.2 nM). In addition, homology modeling of the receptor and docking studies for the most potent compounds were performed, elucidating the binding modes of the fusion molecules and the structure elements contributing to the observed high receptor binding.

Ligand Docking (Cont'd)

New *in silico* insights into the inhibition of RNAP II by α -amanitin and the protective effect mediated by effective antidotes

Juliana Garcia, Alexandra T.P. Carvalho, Daniel F.A.R. Dourado, Paula Baptista, Maria de Lourdes Bastos, Félix Carvalho [University of Porto]

J. Mol.Graph. and Mod., **51**, 120-127, 2014.

Poisonous α -amanitin-containing mushrooms are responsible for the major cases of fatalities after mushroom ingestion. α -Amanitin is known to inhibit the RNA polymerase II (RNAP II), although the underlying mechanisms are not fully understood. The present study provides an *in silico* insight into the inhibition of RNAP II by α -amanitin and also on the interaction of the antidotes on the active site of this enzyme. Docking and molecular dynamics (MD) simulations combined with molecular mechanics-generalized Born surface area method (MM-GBSA) were carried out to investigate the binding of α -amanitin and three antidotes benzylpenicillin, ceftazidime and silybin to RNAP II. Our results reveal that α -amanitin should affect RNAP II transcription by compromising trigger loop (TL) function.

***Ab initio* molecular simulations for proposing novel peptide inhibitors blocking the ligand-binding pocket of urokinase receptor**

Tatsuroh Mizushima, Takuya Sugimoto, Tomoyo Kasumi, Kohta Araki, Hiroshi Kobayashi, Noriyuki Kurita [Toyohashi University of Technology]

J. Mol.Mod., **20**, 2292, 2014.

Recent biochemical experiments have revealed that a variety of proteases play important roles in cancer invasion and metastasis. Among these proteases, urokinase-type plasminogen activator (uPA) is particularly important, since its specific binding to the receptor (uPAR) existing on the surface of a cancer cell is considered to be a trigger for cancer invasion. It is thus expected that the blocking of the binding can inhibit cancer invasion in the cancer patients and improve their prognosis dramatically. In the present study, we propose some peptides composed of these important residues and investigate the specific interactions and the binding affinity between uPAR and the peptides at an electronic level, using *ab initio* molecular simulations.

Insight into the Allosteric Inhibition of Abl Kinase

Anna Lucia Fallacara, Cristina Tintori, Marco Radi, Silvia Schenone, Maurizio Botta [Università degli Studi di Siena]

J.Chem. Infor. and Mod. **54**, 1325–1338, 2014.

Abl kinase inhibitors targeting the ATP binding pocket are currently used as a front-line therapy for the treatment of chronic myelogenous leukemia (CML), but their use has significant limitation because of the development of drug resistance (especially due to the T315I mutation). Two compounds (GNF-2 and BO1) have been found able to inhibit the Abl activity through a peculiar mechanism of action. In order to better understand the mechanism of Abl allosteric inhibition, MD simulations and MM/GBSA analysis were performed on Abl wt and T315I in complex with GNF-2 and BO1, and the results were compared to those found for the natural myristoyl ligand.

Ligand Docking (Cont'd)

Characterization of the divalent metal binding site of bacterial polysaccharide deacetylase using crystallography and quantum chemical calculations

Md Munan Shaik[Institut de Biologie Structurale—Jean-Pierre Ebel], Nicholas Bhattacharjee, Anirban Bhattacharjee, Martin J. Field . Giuseppe Zanotti

Proteins: Stru. Fun. & Bioinf., **82**, 1311–1318, 2014.

Peptidoglycan deacetylase (HP0310, HpPgda) from the gram-negative pathogen *Helicobacter pylori*, is the enzyme responsible for a peptidoglycan modification that counteracts the host immune response. In a recent study, we determined the crystallographic structure of the enzyme, which is a homo-tetramer (Shaik et al., PloS One 2011;6:e19207). The metal-binding site, which is essential for the enzyme's catalytic activity, is visible within the structure, but we were unable to identify the nature of the metal itself. In this study, we have obtained a higher-resolution crystal structure of the enzyme, which shows that the ion bound is, in fact, zinc.

Free energetics of rigid body association of ubiquitin binding domains: A biochemical model for binding mediated by hydrophobic interaction

Di Cui, Shuching Ou , Sandeep Patel [University of Delaware]

Proteins: Stru. Fun. & Bioinf., **82**, 1453–1468, 2014.

Weak intermolecular interactions, such as hydrophobic associations, underlie numerous biomolecular recognition processes. Here, we use atomistic molecular dynamics simulations in conjunction with the Adaptive Biasing Force sampling method to compute potentials of mean force (the reversible work, or free energy, associated with the binding process) to investigate the thermodynamic signature of complexation in this well-studied biochemical model of hydrophobic association.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 51, June, 2014.

- 1-6 **Boosting sensitivity of boron nitride nanotube (BNNT) to nitrogen dioxide by Fe encapsulation**, Yu-qing Zhang, Yue-Jie Liu, Yan-ling Liu, Jing-xiang Zhao [Harbin Normal University]

In the present work, using density functional theory (DFT) methods, we put forward a novel strategy to enhance the sensitivity of BNNT to nitrogen dioxide (NO₂) by the encapsulation of a single Fe atom inside its cavity.

- 7-12 **Design of novel camphane-based derivatives with antimycobacterial activity**, Georgi Stavrakov, Violeta Valcheva, Irena Philipova, Irini Doytchinova [Medical University of Sofia]

See Applications / QSAR.

- 13-26 **Exploring molecular structures, orbital interactions, intramolecular proton-transfer reaction kinetics, electronic transitions and complexation of 3-hydroxycoumarin species using DFT methods**, Nuttawisit Yasarawan, Khajadpai Thipyapong [Burapha University], Vithaya Ruangpornvisuti

See Methodology / QM and QM/MM.

- 27-36 **A single amino acid change humanizes long-chain fatty acid binding and activation of mouse peroxisome proliferator-activated receptor α** Dhawal P. Oswal, Gerald M. Alter, S. Dean Rider Jr., Heather A. Hostetler [Wright State University]

Peroxisome proliferator-activated receptor α (PPAR α) is an important regulator of hepatic lipid metabolism which functions through ligand binding. Despite high amino acid sequence identity (>90%), marked differences in PPAR α ligand binding, activation and gene regulation have been noted across species. The present study was aimed to determine if structural alterations could account for these differences.

- 37-49 **Using thermodynamic integration MD simulation to compute relative protein–ligand binding free energy of a GSK3 β kinase inhibitor and its analogs**, Hsing-Chou Lee, Wen-Chi Hsu, An-Lun Liu, Chia-Jen Hsu, Ying-Chieh Sun [National Taiwan Normal University]

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 50-63 **Mechanistic investigation of the reactivity of disilene with nitrous oxide: A DFT study**, Bholanath Maity, Debasis Koley [Indian Institute of Science Education and Research (IISER) Kolkata]

We have reported the mechanistic investigation of the reaction of N₂O addition to disilene, *trans*-[(TMS)₂N(η^1 -Me₅C₅)Si=Si(η^1 -Me₅C₅)N(TMS)₂] (**1t**), employing density functional theory (BP86/TZVP//BP86/SVP) calculations. The potential energy surfaces of the title reaction are broadly classified under three pathways.

64-72 **Group-based QSAR and molecular dynamics mechanistic analysis revealing the mode of action of novel piperidinone derived protein-protein inhibitors of p53-MDM2** , Sukriti Goyal, Sonam Grover, Jaspreet Kaur Dhanjal, Chetna Tyagi, Manisha Goyal, Abhinav Grover [Banasthali University]

See Applications / QSAR.

73-78 **The nature of interactions in nicotinamide crystal** ,Tomasz Misiaszek, Żaneta Czyżnikowska[Wrocław Medical University]

In this study, we analyze the nature of intermolecular interactions in nicotinamide complexes appearing in conformations found in the crystal structure, including many-body effects. In doing so, we employ symmetry-adapted perturbation theory based on density functional theory description of monomers, and we perform the many-body variational-perturbational interaction energy decomposition.

79-85 **The effect of intermolecular interactions on the charge transport properties of thiazole/thiophene-based oligomers with trifluoromethylphenyl** ,Pages Ling Liu, Guochun Yang [Northeast Normal University], Xiaodan Tang, Yun Geng, Yong Wu, Zhongmin Su

A fundamental understanding of the relationship between intermolecular interactions and transport properties in organic semiconducting materials is significant for their potential applications as electronic device element. Carrier transport properties of thiazole/thiophene-based oligomers with trifluoromethylphenyl groups **1**, **2**, and **3**, in which the type and strength of the intermolecular interactions are different, were investigated within the framework of band model.

86-96 **Effects of substituents on tetracene derivatives on their stabilities and singlet fission** , Li Shen, Yuhua Chen, Xiyong Li [Shandong University,], Jun Gao

In this work, a series of substituted tetracenes were designed to identify tetracene compounds with not only good stability toward oxidation but also small SF activation energies.

97-103 **The inhibitory effect of helenalin on telomerase activity is attributed to the alkylation of the CYS445 residue: Evidence from QM/MM simulations** , Zhiqiang Zhang [Zhengzhou University of Light Industry], Liancai Xu, Hongyeung Cheung

See Applications / Enzyme Catalysis.

104-112 **Identification of a high affinity selective inhibitor of Polo-like kinase 1 for cancer chemotherapy by computational approach** ,Manoj Kumar, Sai Prasad Pydi, Sujata Sharma, Tej P. Singh, Punit Kaur[All India Institute of Medical Sciences, New Delhi]

See Applications / Medicinal Chemistry and Drug Design.

113-119 **A QM/MM study of the catalytic mechanism of aspartate ammonia lyase** , Jing Zhang, Yongjun Liu [Shandong University]

See Applications / Enzyme Catalysis.

- 120-127 **New in silico insights into the inhibition of RNAP II by α -amanitin and the protective effect mediated by effective antidotes** , Juliana Garcia, Alexandra T.P. Carvalho, Daniel F.A.R. Dourado, Paula Baptista, Maria de Lourdes Bastos, Félix Carvalho [University of Porto]

See Methodology / Ligand Docking.

- 128-136 **Quantum chemical characterization of zwitterionic structures: Supramolecular complexes for modifying the wettability of oil–water–limestone system** , Ernesto Lopez-Chavez, Alberto Garcia-Quiroz [de la Universidad Autónoma de la Ciudad de México], Gerardo Gonzalez-Garcia, Gabriela E. Orozco-Duran, Luis S. Zamudio-Rivera, José M. Martinez-Magadan, Eduardo Buenrostro-Gonzalez, Raul Hernandez-Altamirano

In this work, we present a quantum chemical study pertaining to some supramolecular complexes acting as wettability modifiers of oil–water–limestone system.

- 137-148 **Theoretical study of γ -hexachlorocyclohexane and β -hexachlorocyclohexane isomers interaction with surface groups of activated carbon model** , Carlos Enriquez-Victorero, Daniel Hernández-Valdés, Ana Lilian Montero-Alejo, Axelle Durimel, Sarra Gaspard, Ulises Jáuregui-Haza [Instituto Superior de Tecnología y Ciencias Aplicadas]

Activated carbon (AC) is employed in drinking water purification without almost any knowledge about the adsorption mechanism of persistent organic pollutants (POPs) onto it. Hexachlorocyclohexane (HCH) is an organochlorinated contaminant present in water and soils of banana crops production zones of the Caribbean.

Journal of Computational Chemistry, 35 (15), June, 2014.

- 1107–1110 **Toward product control in ring-opening oligomerization of 9H-9-borafluorenes** , Hui Zhu ,Zheng-Wang Qu[Universität Bonn]

To get deep insights into the structure–reactivity relationship for ring-opening oligomerization reactions toward targeted design of novel main-chain boron-containing materials, detailed DFT B97D/TZVP calculations are carried out to compare the ring-opening oligomerization of both unsubstituted and tert-butyl (tBu)-substituted 9H–9-borafluorenes.

- 1111–1121 **Identifying essential pairwise interactions in elastic network model using the alpha shape theory** , Fei Xia, Dudu Tong, Lifeng Yang, Dayong Wang, Steven C. H. Hoi, Patrice Koehl and Lanyuan Lu [Nanyang Technological University]

Elastic network models (ENM) are based on the idea that the geometry of a protein structure provides enough information for computing its fluctuations around its equilibrium conformation. Standard approaches for generating ENs rely on a cutoff distance. There is no consensus on how to choose this cutoff. In this work, we propose instead to filter the set of all residue pairs in a protein using the concept of alpha shapes.

- 1122–1130 **gWEGA: GPU-accelerated WEGA for molecular superposition and shape comparison** , Xin Yan, Jiabo Li [SciNet Technologies], Qiong Gu , Jun Xu

Virtual screening of a large chemical library for drug lead identification requires searching/superimposing a large number of three-dimensional (3D) chemical structures. This article reports a graphic processing unit (GPU)-accelerated weighted Gaussian algorithm (gWEGA) that expedites shape or shape-feature similarity score-based virtual screening.

- 1131–1139 **Toward the understanding of the environmental effects on core ionizations** , Adèle D. Laurent [Université de Nantes] , Vitaly N. Glushkov, Thibaut Very , Xavier Assfeld

Experimental X-ray absorption spectra are extensively used to determine electronic structure of small molecules but remain difficult to exploit for proteins due to the large number of peaks within their spectra. This study presents a systematic methodology to evaluate core-ionization energies (Eion) in proteins with the help of the asymptotic projection approach.

- 1140–1148 **SN1-SN2 and SN2-SN3 mechanistic changes revealed by transition states of the hydrolyses of benzyl chlorides and benzenesulfonyl chlorides** , Shinichi Yamabe [Kyoto University], Guixiang Zeng, Wei Guan ,Shigeyoshi Sakaki

Hydrolysis reactions of benzyl chlorides and benzenesulfonyl chlorides were theoretically investigated with the density functional theory method, where the water molecules are explicitly considered.

- 1149–1158 **Using operators to expand the block matrices forming the Hessian of a molecular potential** ,Martin Carlsen[Technical University of Denmark]

We derive compact expressions of the second-order derivatives of bond length, bond angle, and proper and improper torsion angle potentials, in terms of operators represented in two orthonormal bases.

- 1159–1164 **Transferable pseudoclassical electrons for aufbau of atomic ions** , Solen Ekesan, Seyit Kale, Judith Herzfeld [Brandeis University]

Generalizing the LEWIS reactive force field from electron pairs to single electrons, we present LEWIS• in which explicit valence electrons interact with each other and with nuclear cores via pairwise interactions.

Journal of Computational Chemistry, 35 (16), June, 2014.

- 1165–1198 **Modeling biophysical and biological properties from the characteristics of the molecular electron density, electron localization and delocalization matrices, and the electrostatic potential** , Chérif F. Matta [Mount Saint Vincent University]

The electron density and the electrostatic potential are fundamentally related to the molecular hamiltonian, and hence are the ultimate source of all properties in the ground- and excited-states. The advantages of using molecular descriptors derived from these fundamental scalar fields, both accessible from theory and from experiment, in the formulation of quantitative structure-to-activity and structure-to-property relationships, collectively abbreviated as QSAR, are discussed.

- 1199–1207 **A multiple time step scheme for multiresolved models of Macromolecules** , Nicodemo Di Pasquale, Richard J. Gowers , Paola Carbone [The University of Manchester]

In hybrid particle models where coarse-grained beads and atoms are used simultaneously, two clearly separate time scales are mixed. If such models are used in molecular dynamics simulations, a multiple time step (MTS) scheme can therefore be used. In this manuscript, we propose a simple MTS algorithm which approximates for a specific number of integration steps the slow coarse-grained bead–bead interactions with a Taylor series approximation while the atom–atom ones are integrated every time step.

- 1208–1218 **Systematic implicit solvent coarse graining of dimyristoylphosphatidylcholine lipids** , Alexander Mirzoev [Stockholm University] , Alexander P. Lyubartsev

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 1219–1239 **All-atom polarizable force field for DNA based on the classical drude oscillator model** , Alexey Savelyev , Alexander D. MacKerell Jr.[University of Maryland,]

See Applications / Nucleic Acids.

- 1240–1247 **On the induced-fit mechanism of substrate-enzyme binding structures of nylon-oligomer hydrolase** , Takeshi Baba [University Toyonaka] , Ryuhei Harada, Masayoshi Nakano , Yasuteru Shigeta

We present a detailed computational investigation of the induced-fit motion in a nylon-oligomer hydrolase (NylB) upon substrate binding.

- 1248–1254 **Surface electronic structure calculations using the MBJLDA potential: Application to Si(111)2 × 1** , Phillip V. Smith [The University of Newcastle], Marian W. Radny , G. Ali Shah

The Si(111)2 × 1 surface has been widely studied via a range of different experimental and theoretical techniques, and found to adopt a π -bonded chain configuration. In this article, we show that the MBJLDA approach, originally proposed by Tran and Blaha for bulk materials (Tran and Blaha, Phys. Rev. Lett. 2009, 102, 226401), yields results which are comparable to GW, and generally superior to those obtained from hybrid functional density functional theory calculations.

- 1255–1260 **WATsite: Hydration site prediction program with PyMOL interface** , Bingjie Hu , Markus A. Lill [Purdue University]

See Applications / Water and Solvation.

Journal of Computational Chemistry, 35 (17), June, 2014.

- 1261–1269 **Analyzing the electric response of molecular conductors using “electron deformation” orbitals and occupied-virtual electron transfer** , Marcos Mandado [University of Vigo] , Nicolás Ramos-Berdullas

The concept of “electron deformation orbitals” (EDOs) is used to investigate the electric response of conducting metals and oligophenyl chains.

- 1270–1277 **Moving of fullerene between potential wells in the external icosahedral shell** ,Olga E. Glukhova [Saratov State University], Anna S. Kolesnikova, Michael M. Slepchenkov , Vladislav V. Shunaev

The results of the theoretical investigation of the behavior of fullerenes C20 and C60 inside the icosahedral external shell on example of carbon nanoclusters, C20@C240 and C60@C540, are presented in this article.

- 1278–1289 **New force field parameters for metalloproteins I: Divalent copper ion centers including three histidine residues and an oxygen-ligated amino acid residue** ,Olivia Wise , Orkid Coskuner [The University of Texas at San Antonio]

Transition metal ion complexation with proteins is ubiquitous across such diverse fields as neurodegenerative and cardiovascular diseases and cancer. In this study, the structures of divalent copper ion centers including three histidine and one oxygen-ligated amino acid residues and the relative binding affinities of the oxygen-ligated amino acid residues with these metal ion centers, which are debated in the literature, are presented.

- 1290–1301 **Interaction of aromatic units of amino acids with guanidinium cation: The interplay of $\pi\cdots\pi$, $X\cdots\pi$, and $M\cdots\pi$ contacts** ,Alba Campo-Cacharrón [Universidade de Santiago de Compostela] , Enrique M. Cabaleiro-Lago, Jorge A. Carrazana-García , Jesús Rodríguez-Otero

Complexes formed by guanidinium cation and a pair of aromatic molecules among benzene, phenol, or indole have been computationally studied to determine the characteristics of the cation $\cdots\pi$ interaction in ternary systems modeling amino acid side chains. Guanidinium coordinates to the aromatic units preferentially in the following order: indole, phenol, and benzene.

- 1302–1316 **Ab initio path-integral calculations of kinetic and equilibrium isotope effects on base-catalyzed RNA transphosphorylation models** , Kin-Yiu Wong [Hong Kong Baptist University], Yuqing Xu and Darrin M. York

See Methodology / QM and QM/MM.

- 1317–1329 **Efficient 3D kinetic monte carlo method for modeling of molecular structure and dynamics** ,Mikhail Panshenskov, Ilia A. Solov'yov [University of Southern Denmark] , Andrey V. Solov'yov

See Applications / Protein Dynamics.

- 1330–1337 **The READY program: Building a global potential energy surface and reactive dynamic simulations for the hydrogen combustion** ,César Mogo [Centro de Investigação em Química do Algarve Universidade do Algarve] ,João Brandão

See Applications / Bioinformatics.

Journal of Molecular Modeling, 20 (6), June, 2014.

- 2313 **Theoretical study of CO oxidation on cationic, neutral, and anionic AuM dimers (M = Pd and Ag) ,** Xuan Chen, Rui-Feng Lu [Nanjing University of Science and Technology], Er-Jun Kan, Yu-Zhen Liu, Chuan-Yun Xiao, Kai-Ming Deng

The CO and O₂ adsorption as well as CO oxidation on cationic, neutral, and anionic AuM dimers (M = Pd, Ag) are studied by density functional calculations. Our results show that CO and O₂ are adsorbed more stably on AuPd dimers than on AuAg dimers with corresponding charge state.

- 2308 **Structures of TraI in solution ,** Nicholas J. Clark, Madushi Raththagala, Nathan T. Wright, Elizabeth A. Buenger, Joel F. Schildbach, Susan Krueger, Joseph E. Curtis [National Institute of Standards and Technology]

See methodology / Homology Modeling.

- 2307 **Theoretical prediction of the mechanisms for defect healing or oxygen doping in a hexagonal boron nitride (*h*-BN) sheet with nitrogen vacancies by NO₂ molecules ,** Jing-wen Feng, Yue-Jie Liu, Jing-xiang Zhao [Harbin Normal University]

Healing defects in hexagonal boron nitride (*h*-BN sheet) or doping it with oxygen can modify or restore its physical properties, which would increase its range of potential applications. In this work, using density functional theory (DFT) calculations, we identified a mechanism for healing *h*-BN sheets with nitrogen vacancies (V_N) or doping BN sheets with oxygen using NO₂ molecules.

- 2303 **DFT investigation of the mismatched base pairs (T-Hg-T)₃, (U-Hg-U)₃, d(T-Hg-T)₂, and d(U-Hg-U)₂** , Tiziana Marino [Università della Calabria]

Mismatched T:T and U:U base pairs in DNA and RNA duplexes represent the preferred target for mercury(II) cations. In this work, the structural, energetic, and electronic properties of the metallo base pairs T-Hg-T and U-Hg-U were investigated using density functional theory.

- 2302 **Theoretical study of methyl group transfer assisted by proton transfer reaction in the N-acylated imidates,** Rezika Larabi, Soraya Abtouche, Meziane Brahimi [Faculté de Chimie, USTHB]

The single methyl group transfer (MGT), double MGT and single MGT assisted by proton transfer (PT) that occurs in small biological systems N-methoxy methylene formamide and N-hydroxy methylen formamide (NMMF–NHMF) have been investigated completely in the present study using density functional theory (DFT) and Möller-Plesset perturbation (MP2) methods with a 6-31G(d) basis set.

- 2300 **Franck–Condon factors using supervised artificial neural networks. I. The CF⁺ cation ,** Lourdes Sandoval [Facultad de Ciencias de la Computación, BUAP], José M. Amero, Gabriel J. Vazquez, Alejandro Palma

Several studies of the electronic and vibrational structure of CF⁺ have been performed since this molecule was first discovered to occur in the interstellar medium, and even before that. In this work, an analysis of all of the potential energy curves of CF⁺ that were candidates for this kind of calculation was undertaken.

- 2294 **Redox properties of biscyclopentadienyl uranium(V) imido-halide complexes: a relativistic DFT study**, Aziz Elkechai, Farida Kias, Fazia Talbi, Abdou Boucekkine [Campus de Beaulieu]

Calculations of ionization energies (IE) and electron affinities (EA) of a series of biscyclopentadienyl imido-halide uranium(V) complexes $Cp^*_2U(=N-2,6-iPr_2-C_6H_3)(X)$ with $X = F, Cl, Br, \text{ and } I$, related to the U^{IV}/U^V and U^V/U^{VI} redox systems, were carried out, for the first time, using density functional theory (DFT) in the framework of the relativistic zeroth order regular approximation (ZORA) coupled with the conductor-like screening model (COSMO) solvation approach.

- 2293 **NMR and quantum chemical analysis of 3-(2-methly-2-phenylhydrazinyl)cyclohex-2-en-1-one**, Zsófia Dubrovay [Eötvös University], Péter G. Szalay

Two-dimensional representation of a molecular structure is in some cases misleading, since it may not correctly represent important details and may not provide adequate information on the electronic structure of the molecule. In this article the NMR and quantum chemical analysis of the title compound 3-(2-methly-2-phenylhydrazinyl)cyclohex-2-en-1-one will be presented.

- 2292 **Ab initio molecular simulations for proposing novel peptide inhibitors blocking the ligand-binding pocket of urokinase receptor**, Tatsuroh Mizushima, Takuya Sugimoto, Tomoyo Kasumi, Kohta Araki, Hiroshi Kobayashi, Noriyuki Kurita [Toyohashi University of Technology]

See Methodology / Ligand Docking.

- 2291 **Halogen bonds enhanced by σ -hole and π -hole interactions: a comparative study on cooperativity and competition effects between $X\cdots N$ and $S\cdots N$ interactions in $H_3N\cdots XCN\cdots SF_2$ and $H_3N\cdots XCN\cdots SO_2$ complexes ($X = F, Cl, Br \text{ and } I$)**, Mehdi D. Esrafilii [University of Maragheh], Mahshad Vakili

In this work, the $H_3N\cdots XCN\cdots SF_2$ and $H_3N\cdots XCN\cdots SO_2$ ($X = F, Cl, Br, I$) complexes are theoretically investigated to find ways to enhance the halogen bond interaction. Cooperative effects are found when $X\cdots N$ and $S\cdots N$ bonds coexist in the same complex.

- 2290 **Deamination features of 5-hydroxymethylcytosine, a radical and enzymatic DNA oxidation product**, André Grand, Nelly Jorge, Christophe Morell, Jean Cadet, Leif A. Eriksson [University of Gothenburg]

See Applications / Nucleic Acids.

- 2287 **All-atom structures and calcium binding sites of the bacterial photosynthetic LH1-RC core complex from *Thermochromatium tepidum***, Maria G. Khrenova, Alexander V. Nemukhin [Lomonosov Moscow State University], Bella L. Grigorenko, Peng Wang, Jian-Ping Zhang

Computationally derived structures of the photosynthetic core complex composed of the light-harvesting (LH) system LH1 and the reaction center (RC) from a thermophilic purple sulfur bacterium *Thermochromatium tepidum* are reported providing first models of the LH1 system at atomic resolution. We used the known primary structure of α and β polypeptides from this particular LH1 complex and the related bacterial LH templates to design the LH1 torus composed of 16 $\alpha\beta$ subunits trapping bacteriochlorophyll (BChl-a) dimers and carotenoid molecules.

- 2286 **Atom-based 3D-QSAR, molecular docking and molecular dynamics simulation assessment of inhibitors for thyroid hormone receptor α and β** , Manish Kumar Gupta [Chhatrapati Shahu Ji Maharaj University], Krishna Misra

See Applications / QSAR.

- 2283 **REMD and umbrella sampling simulations to probe the energy barrier of the folding pathways of engrailed homeodomain**, Vinod Jani, Uddhaves B. Sonavane, Rajendra Joshi [Pune University Campus Ganeshkhind]

See Applications / Protein Floding.

- 2281 **Fingerprints in IR OH vibrational spectra of H₂O clusters from different H-bond conformations by means of quantum-chemical computations**, Yuan Liu, Lars Ojamäe [Linköping University]

The thermodynamic stabilities and IR spectra of the three water clusters (H₂O)₂₀, (H₂O)₅₄, and (H₂O)₁₀₀ are studied by quantum-chemical computations.

- 2279 **Performance of four different force fields for simulations of dipeptide conformations: GlyGly, GlyGly⁻, GlyGly · Cl⁻, GlyGly · Na⁺ and GlyGly · (H₂O)₂**, Chen Dong, Li Yong-Zhi, Wei Zhi-Chao, Liu Bo [Henan University]

See Applications / Protein Confirmationnal Analysis.

- 2278 **AllerTOP v.2—a server for in silico prediction of allergens**, Ivan Dimitrov, Ivan Bangov, Darren R. Flower, Irini Doytchinova [Medical University of Sofia]

We report a set of novel models for allergen prediction utilizing amino acid *E*-descriptors, auto- and cross-covariance transformation, and several machine learning methods for classification, including logistic regression (LR), decision tree (DT), naïve Bayes (NB), random forest (RF), multilayer perceptron (MLP) and knearest neighbours (*k*NN). The best performing method was *k*NN with 85.3 % accuracy at 5-fold cross-validation.

- 2277 **Intermediate electrostatic field for the elongation method**, Piotr Kuźniarowicz, Kai Liu, Yuriko Aoki, Feng Long Gu, Anna Stachowicz, Jacek Korchowiec [Jagiellonian University]

A simple way to improve the accuracy of the fragmentation methods is proposed. The formalism was applied to the elongation (ELG) method at restricted open-shell Hartree-Fock (ROHF) level of theory.

- 2274 **DFT and MD study of the divalent-cation-mediated interaction of ochratoxin A with DNA nucleosides**, Jozef Motyčka, Pavel Mach[Comenius University in Bratislava], Milan Melicherčík, Jan Urban

See Applications / Membrane proteins and Lipid-Peptide Interactions.

- 2273 **Effect of explicit water molecules on ligand-binding affinities calculated with the MM/GBSA approach**, Paulius Mikulskis, Samuel Genheden, Ulf Ryde [Lund University]

See Applications / Water and Solvation.

- 2272 **On the origin of internal rotation in ammonia borane** , Monika Parafiniuk, Mariusz P. Mitoraj [Jagiellonian University]

The internal rotation in ammonia borane (AB) was studied on the basis of natural orbitals for chemical valence (NOCV) and eigenvectors for Pauli repulsion (NOPR). We found that the total hyperconjugation stabilization (ca. 5 kcal mol⁻¹), based on the charge transfer from the occupied σ (B–H) orbitals into the empty σ^* (N–H), slightly favors the staggered conformation over the eclipsed one; however, the barrier to internal rotation in ammonia borane can be understood predominantly in a ‘classical’ way, as originating from the steric (Pauli) repulsion contributions (of the kinetic origin) that act solely between N–H and B–H bonds.

- 2271 **Analyses of cobalt–ligand and potassium–ligand bond lengths in metalloproteins: trends and patterns** Natércia F. Brás, António J. M. Ribeiro, Marina Oliveira, Nathália M. Paixão, Juan A. Tamames, Pedro A. Fernandes, Maria J. Ramos [Universidade do Porto,]

Cobalt and potassium are biologically important metal elements that are present in a large array of proteins. Here, we report a thorough analysis of the geometric properties of cobalt and potassium coordination spheres that was performed with high resolution on a representative set of structures from the Protein Data Bank and complemented by quantum mechanical calculations realized at the DFT level of theory (B3LYP/ SDD) on mononuclear model systems.

- 2269 **A computational study on 4,7-di(furan-2-yl)benzo[c][1,2,5]thiadiazole monomer and its oligomers** , Hakan Kayi [Atılım University]

The energy gap, E_g , between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energy levels that determines the electronic and optical properties of 4,7-di(furan-2-yl)benzo[c][1,2,5]thiadiazole (FSF) polymer is calculated by performing quantum chemical calculations.

- 2268 **Interaction of β -cyclodextrin as catalyst with acetophenone in asymmetric reaction: a theoretical survey** , Yali Wan, Xueye Wang [Xiangtan University], Na Liu

See Applications / Enzyme Catalysis.

- 2267 **Molecular dynamics study of the adsorption of anionic surfactant in a nonionic polymer brush** , Hua Wang, Heng Zhang, Shiling Yuan, Chengbu Liu, Zhen Xu [Qilu University of Technology]

See Applications / Surface, Catalyst and materials subjects.

- 2266 **Virtual screening of traditional Chinese medicine (TCM) database: identification of fragment-like lead molecules for filariasis target asparaginyl-tRNA synthetase** , Hemant Arya, Mohane Selvaraj Coumar [Pondicherry University]

See Applications / Medicinal Chemistry and Drug Design.

- 2265 **Menshutkin reaction between DABCO and benzyfluoride/fluorodiphenylmethane: a mechanistic study** , Amritpal Singh, Neetu Goel [Panjab University]

The microcosmic mechanism of the Menshutkin reaction between DABCO and benzyl fluoride/fluorodiphenylmethane has been investigated in both the gas and solvent phase by performing DFT calculations at B3LYP/6-31G(d,p) level of theory.

- 2264 **Adsorption behaviors of monomer and dimer of formic acid on Pt (111) in the absence and presence of water** , Yuanyuan Qi, Rongxiu Zhu, Dongju Zhang[Shandong University]

By performing density functional theory (DFT) theory calculations, we studied the adsorption behaviors of the monomer and dimer of formic acid (HCOOH, FA) on the Pt(111) surface with and without the presence of water molecules.

- 2263 **Cluster solvation models of carbon nanostructures: extension to fullerenes, tubes, and buds** , Francisco Torrens[Universitat de València], Gloria Castellano

Carbon nanobud (CNB), a hybrid material consisting of single-wall C-nanotubes (CNTs) (SWNTs) with covalently attached fullerenes, in cluster form is discussed in organic solvents. Theories are developed based on *bundlet* and droplet models describing size-distribution functions.

- 2262 **Reaction of chlorine radical with tetrahydrofuran: a theoretical investigation on mechanism and reactivity in gas phase** , Samiyara Begum, Ranga Subramanian [Indian Institute of Technology, Patna]

Reaction of chlorine (Cl) radical with heterocyclic saturated ether, tetrahydrofuran has been studied. The detailed reactivity and mechanism of this reaction is analyzed using hybrid density functional theory (DFT), B3LYP and BB1K methods, and aug-cc-pVTZ basis set. To explore the mechanism of the reaction of tetrahydrofuran with Cl radical, four possible sites of hydrogen atom (H) abstraction pathways in tetrahydrofuran were analyzed.

- 2261 **Theoretical studies on a new high energy density compound 6-amino-7-nitropyrzino[2,3-e][1,2,3,4]tetrazine 1,3,5-trioxide (ANPTTO)** , Tianyi Wang, Chunmei Zheng, Junqing Yang, Xueli Zhang, Xuedong Gong[Nanjing University of Science and Technology], Mingzhu Xia

The derivatives of 1,2,3,4-tetrazine may be promising candidates for high-energy density compounds and are receiving more and more attentions. In this study, a new derivative 6-amino-7-nitropyrzino[2,3-e][1,2,3,4]tetrazine 1,3,5-trioxide (ANPTTO) has been designed.

- 2259 **Ab initio analysis on the interaction of CO₂ binding to peracetated D-glucopyranose** , Chang Honghong, Yang Congcong, Li Xing, Wei Wenlong, Pang Xianrong[Taiyuan University of Technology], Qiao Yan

CO₂-philes can be utilized as additives, surfactants, and a potential phase-change physical solvent or absorbent for CO₂, so the design and synthesis of CO₂-philes typically non-fluorous compounds is important to develop more application areas of CO₂. In order to study the interaction properties between sugar acetates with CO₂, 1,2-di-O-acetyl- α -D-glucopyranose and 1,2-di-O-acetyl- β -D-glucopyranose were decided as substrates after

initial chemical stimulations with peracetated D-glucopyranose, and the complex model was one CO₂ molecule combined with one sugar substrate (1:1).

- 2258 **An efficient ab initio DFT and PCM assessment of the potentiometric selectivity of a salophen type Schiff base** , Serkan Demir[Ondokuz Mayıs University], Hakan Yilmaz, Maowulidan Dilimulati, Müberra Andaç

As a neutral carrier component for the preparation of a potentiometric membrane sensor, the affinity and selectivity of the salophen type Schiff base ligand obtained by 1:2 condensation of 2,3-diaminopyridine with salicylaldehyde toward a series of common cations has been fully examined by DFT/B3LYP and integral equation formalism polarizable continuum model (IEF-PCM or only given with PCM as default input in the computations) in combination with the experimental data.

- 2257 **Mutatomics analysis of the systematic thermostability profile of *Bacillus subtilis* lipase A** , Feifei Tian, Cao Yang, Congcong Wang, Tailin Guo, Peng Zhou [University of Electronic Science and Technology of China (UESTC)]

Use of point mutagenesis technique to improve protein thermostability is a routine strategy in the protein engineering community and directed evolution approach has been widely utilized to fulfill this. In the current study, we performed mutatomics analysis of the systematic thermostability profile of *Bacillus subtilis* lipase A (LipA) using a virtual scanning strategy.

- 2255 **Mechanistic details for anthraniloyl transfer in PqsD: the initial step in HHQ biosynthesis** , Michael C. Hutter[Saarland University], Christian Brengel, Matthias Negri, Claudia Henn, Christina Zimmer, Rolf W. Hartmann, Martin Empting, Anke Steinbach

See Applications / Protein Structure Analysis.

- 2254 **Theoretical insight into the mechanism for the inhibition of the cysteine protease cathepsin B by 1,2,4-thiadiazole derivatives** ,Mauricio Angel Vega-Tejido [Universidad de la República], Sarah El Chamy Maluf, Camila Ramalho Bonturi, Julio Ricardo Sambrano, Oscar N. Ventura

See Applications / Medicinal Chemistry and Drug Design.

- 2253 **Computational screening of oxetane monomers for novel hydroxy terminated polyethers** , Radhakrishnan Sarangapani [High Energy Materials Research Laboratory, Pune], Vikas D. Ghule, Arun K. Sikder

Energetic hydroxy terminated polyether prepolymers find paramount importance in search of energetic binders for propellant applications. In the present study, density functional theory (DFT) has been employed to screen the various novel energetic oxetane derivatives, which usually construct the backbone for these energetic polymers.

- 2241 **Molecular design of donor-acceptor dyes for efficient dye-sensitized solar cells I: a DFT study**, Reda M. El-Shishtawy[King Abdulaziz University], Abdullah M. Asiri, Saadullah G. Aziz, Shaaban A. K. Elroby

Dye-sensitized solar cells (DSSCs) have drawn great attention as low cost and high performance alternatives to conventional photovoltaic devices. The molecular design presented in this work is based on the use of pyran type dyes as donor based on frontier molecular orbitals (FMO) and theoretical UV-visible spectra in combination with squaraine type dyes as an acceptor.

- 2234 **Geometric consequences of electron delocalization for adenine tautomers in aqueous solution**, Ewa D. Raczynska Warsaw University of Life Sciences (SGGW), Mariusz Makowski

Geometric consequences of electron delocalization were studied for all possible adenine tautomers in aqueous solution by means of *ab initio* methods {PCM(water)//DFT(B3LYP)/6-311+G(d,p)} and compared to those in the gas phase {DFT(B3LYP)/6-311+G(d,p)}.

- 2232 **Quantum chemical study of atmospheric aggregates: $\text{HCl}\cdot\text{HNO}_3\cdot\text{H}_2\text{SO}_4$** , Marian Verdes [Universidad Autónoma de Madrid], Miguel Paniagua

HCl, HNO_3 and H_2SO_4 are implicated in atmospheric processes in areas such as polar stratospheric clouds in the stratosphere. Ternary complexes of HCl, HNO_3 and H_2SO_4 were investigated by *ab initio* calculations at B3LYP level of theory with aug-cc-pVTZ and aug-cc-pVQZ basis sets, taking into account basis set superposition error (BSSE).

- 2224 **Theoretical study of the gas-phase thermolysis of 3-methyl-1,2,4,5-tetroxane**, Mariela Inés Profeta, Jorge Marcelo Romero, Nelly Lidia Jorge, André Grand, Alfonso Hernández-Laguna[Instituto Andaluz de Ciencias de la Tierra (UGR-CSIC)]

Cyclic organic peroxides are a broad and highly sought-after class of peroxide compounds that present high reactivity and even explosive character. The unusually high reactivity of these peroxides can generally be attributed to the rupture of O–O bonds. DFT at the 6-311 + G** level of theory using the BHANDHLYP correlation–exchange functional was applied via the Gaussian09 program to calculate the critical points of the potential energy surface (PES) of this reaction.

- 2222 **Quartic canonical force field in curvilinear internal coordinates for $\text{XY}_3 (D_{3h})$ molecules. The case of the BH_3 molecule**, Consuelo Rosales Ródenas [Universidad de Jaén], Juana Vázquez Quesada, Emilio Martínez Torres, Juan Jesús López González

Using the canonical force field theory, expressions of quadratic, cubic, and quartic canonical force constants are obtained for $\text{XY}_3 (D_{3h})$ molecules in curvilinear redundant coordinates, i.e., simple valence internal coordinates (VICs), in terms of force constants in normal coordinates and in independent symmetry coordinates.

- 2194 **A study of interaction potentials for H_2 adsorption in Single Walled Nano Tubes: a possible way to more realistic predictions** , Marco Lerario, Alexandre L. Magalhães University of Porto]

A comparative analysis of interaction potentials, classified according to the parametrization method, namely Lorentz-Berthelot rules, semi-empirical or *ab initio* calculations, found their energy depths to scale, respectively, to *ca* 30K, *ca* 40K, and *ca* 60K. Our results suggest a pressure range for convenient H_2 storage and enlighten the influence of CNT size on adsorption performance. In addition, larger CNTs are capable to host further hydrogen layers, but only at very high pressures.

- 2175 **Electron density analysis of 1-butyl-3-methylimidazolium chloride ionic liquid** , Lourdes del Olmo [Universidad Autónoma de Madrid], Cercis Morera-Boado, Rafael López, José M. García de la Vega

An analysis of the electron density of different conformers of the 1-butyl-3-methylimidazolium chloride (bmimCl) ionic liquid by using DFT through the BVP86 density functional has been obtained within the framework of Bader's atom in molecules (AIM), localized orbital locator (LOL), natural bond orbital (NBO), and deformed atoms in molecules (DAM).

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1 APPLICATIONS (144) Page 2

1.1 Small Molecules (17)

Water and Solvation	Page 2	QSAR	Page 6
Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 7

1.2 Biopolymers (127)

Bioinformatics and Cheminformatics	Page 7	Ligand Binding	Page 23
Protein Sequence Analysis	Page 8	Enzyme Catalysis	Page 27
Protein Secondary Structure	Page 9	Protein-Protein Interactions	Page 29
Comparative or Homology Modeling	Page 10	Membrane Proteins	Page 30
Protein Conformational Analysis	Page 11	Protein Folding	Page 34
Protein Structure Analysis	Page 14	Protein-Nucleic Acids	Page 36
Protein Dynamics	Page 16	Nucleic Acids	Page 37
Free Energy Calculations	Page 22		

1.3 Polymers

1.4 Surfaces, Catalysts and Material Page 39

2 METHODOLOGY (21) Page 39

Potentials and Parameters	Page 39	QM & QM/MM	Page 41
Molecular Dynamics	Page 40	Comparative or Homology	Page 43
Free Energy Perturbation	Page 41	Ligand Docking	Page 44

3 JOURNAL REVIEWS (8) Page 46

Journal of Molecular Graphics and Modeling, 52, July, 2014.
 Journal of Molecular Modeling, 20 (7, 8), July, 2014.
 Journal of Computational Chemistry, 35 (18, 19), July, 2014.
 Journal of Computational Chemistry, 35 (20, 21, 22), August, 2014.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 72

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Thermodynamics of Water in an Enzyme Active Site: Grid-Based Hydration Analysis of Coagulation Factor Xa

Crystal N. Nguyen, Anthony Cruz, Michael K. Gilson, Tom Kurtzman [The City University of New York]

J. Chem. Theor. and Comp., **10**, 2769–2780, 2014.

Water molecules in the active site of an enzyme occupy a complex, heterogeneous environment, and the thermodynamic properties of active-site water are functions of position. As a consequence, it is thought that an enzyme inhibitor can gain affinity by extending into a region occupied by unfavorable water or lose affinity by displacing water from a region where it was relatively stable. Recent advances in the characterization of binding-site water, based on the analysis of molecular simulations with explicit water molecules, have focused largely on simplified representations of water as occupying well-defined hydration sites.

Medicinal Chemistry and Drug Design

A possible solution for hair loss by inhibiting corticotropin-releasing factor (CRF) receptor from traditional Chinese medicine

Hung-Jin Huang, Calvin Yu-Chian Chen [Asia University]

J. Biomol. Stru. and Dyn., **32**, 1613-1623, 2014.

Corticotropin-releasing factor (CRF) and corticotropin-releasing factor receptor (CRFR) play important roles in stress response, including anxiety and depression syndrome. The CRF expression also relates to chronic stress-related hair loss. This study utilizes the world's largest traditional Chinese medicine (TCM) database and molecular dynamics (MD) simulations to investigate novel CRFR inhibitors for treatment of alopecia. The docking and screening from TCM database results indicate the vitamin B2, 3 beta-isodihydrocadambine, and caribine display higher binding affinity than maltose in maltose binding protein.

 MMCC Results 8013 Los Sabalos Street San Diego, CA 92126 Tel. (858) 663-0162 e-mail: mmccresults@gmail.com Dr. R. Mutyala. RR Labs Inc., 8013 Los Sabalos St. San Diego, CA 92126 Editors Emeritus: Bruce Gelin, Ph.D. David Busath, M.D. Dr. Gelin was founder of MMCC Results and edited volumes 1-6. Dr. David Busath edited volumes 7-14	MMCC Results (ISSN 1061-6381) is published ten times per year at the beginning of each month except January and August by the independent business, MMCC Results. Mention of software, hardware, or other products is for informational purposes only and does not constitute an endorsement or recommendation by MMCC Results nor by the authors of the paper cited. All product names are the trademarks or registered symbols of their respective holders. Marginal symbols indicate that the authors acknowledged the use of a software package from a commercial source. A refers to Accelrys Inc. and T to Tripos Inc. Other companies are denoted by their name in a box. Papers of special interest are marked by an exclamation point [!]. Copyright © 2006 MMCC Results	Assistant Editors: Sowmya .N Rational Labs, Hyderabad., India Sambasivareddy M RR Labs Inc., San Diego, CA.

Medicinal Chemistry and Drug Design (Cont'd)

In silico* characterization and molecular dynamics simulation of Pfcyc-1, a cyclin homolog of *Plasmodium falciparum

Abhinav Kaushik, Sangeetha Subramaniam, Dinesh Gupta [International Centre for Genetic Engineering and Biotechnology]

J. Biomol. Stru. and Dyn., 32, 1624-1633, 2014.

Malaria is still one of the deadly diseases resulting in deaths of millions of people worldwide and situation has become worse due to alarming rise in anti-malarial drug resistance. We have investigated the structure and dynamics of Pfcyc-1 structural model by performing 10 ns molecular dynamics (MD) simulation. Our study indicates that despite poor sequence similarities with cyclin H and A, the characteristic structural cyclin domains are conserved in Pfcyc-1 too. The Pfcyc-1 model reveals a cyclin box, consisting of two tandemly repeating five-helix bundles separated by a linker hinge peptide.

Interactions of selected indole derivatives with COX-2 and their *in silico* structure modifications towards the development of novel NSAIDs

K.V. Dileep, C. Remya, I. Tintu, C. Sadasivan [Kannur University]

J. Biomol. Stru. and Dyn., 32, 1855-1863, 2014.

Cyclooxygenase-2 (COX-2) is an important enzyme responsible for the formation of potent inflammatory mediators like prostaglandins, prostacyclin and thromboxane. Hence, inhibition of COX-2 is one of the best ways to control the inflammation. Non-steroidal anti-inflammatory drugs can control inflammation by inhibiting Cyclooxygenase. Selective inhibition of COX-2 is preferable over the inhibition of COX-1 because of the fewer adverse effects produced. Molecular modeling and docking of 134 selected indole compounds were done against COX-2. The pharmacophore-based *in silico* structural modifications of the best scored compounds were carried out in order to enhance the binding affinity and selectivity.

2-Hexylthio- β,γ -CH₂-ATP is an Effective and Selective NTPDase2 Inhibitor

Irina Gillerman, Joanna Lecka, Luba Simhaev, Mercedes N. Munkonda, Michel Fausther, Mireia Martín-Satué, Hanoch Senderowitz, Jean Sévigny, Bilha Fischer [Bar-Ilan University]

J. Med. Chem., 57, 5919–5934, 2014.

NTPDase2 catabolizes nucleoside triphosphates and consequently, through the interaction of nucleotides with P₂ receptors, controls multiple biological responses. NTPDase2 inhibitors could modulate responses induced by nucleotides in thrombosis, inflammation, cancer, etc. Here we developed a set of ATP analogues as potential NTPDase inhibitors and identified a subtype-selective and potent NTPDase2 inhibitor, 2-hexylthio- β,γ -methylene-ATP, 2. Analogue 2 was stable to hydrolysis by NTPDase1, -2, -3, and -8. It inhibited hNTPDase2 with K_i 20 μ M, while only marginally (5–15%) inhibiting NTPDase1, -3, and -8. Homology models of hNTPDase1 and -2 were constructed.

Medicinal Chemistry and Drug Design (Cont'd)

Ensemble pharmacophore meets ensemble docking: a novel screening strategy for the identification of RIPK1 inhibitors

S. M. Fayaz, G. K. Rajanikant [National Institute of Technology Calicut,]

J. Comp. Aided. Mol. Design, **28**, 779-794, 2014.

Necroptosis, a programmed form of necrotic cell death, has been implicated in many diseases including neurological disorders. Receptor interacting serine/threonine protein kinase 1 (RIPK1) is an important regulatory protein involved in the necroptosis and inhibition of this protein is essential to stop necroptotic process and eventually cell death. Current structure-based virtual screening methods involve a wide range of strategies and recently, considering the multiple protein structures for pharmacophore extraction has been emphasized as a way to improve the outcome. . In this study, dual ensemble screening, a novel computational strategy was used to identify diverse and potent inhibitors against RIPK1.

Modeling a Crowdsourced Definition of Molecular Complexity

Robert P. Sheridan [Merck Research Laboratories], Nicolas Zorn, Edward C. Sherer, Louis-Charles Campeau, Charlie (Zhenyu) Chang, Jared Cumming, Matthew L. Maddess, Philippe G. Nantermet, Christopher J. Sinz, Paul D. O'Shea

J.Chem. Infor. and Mod. **54**, 1325–1338, 2014.

This paper brings together the concepts of molecular complexity and crowdsourcing. An exercise was done at Merck where 386 chemists voted on the molecular complexity (on a scale of 1–5) of 2681 molecules taken from various sources: public, licensed, and in-house. The meanComplexity of a molecule is the average over all votes for that molecule. As long as enough votes are cast per molecule, we find meanComplexity is quite easy to model with QSAR methods using only a handful of physical descriptors (e.g., number of chiral centers, number of unique topological torsions, a Wiener index, etc.).

Binding Free-Energy Calculation Is a Powerful Tool for Drug Optimization: Calculation and Measurement of Binding Free Energy for 7-Azaindole Derivatives to Glycogen Synthase Kinase-3 β

Kunihiro Kitamura[Nihon Pharmaceutical University], Yunoshin Tamura, Tomokazu Ueki, Koji Ogata, Shigeho Noda, Ryutaro Himeno, Hiroshi Chuman

J.Chem. Infor. and Mod. **54**, 1653–1660, 2014.

Present computational lead (drug)-optimization is lacking in thermodynamic tactics. To examine whether calculation of binding free-energy change (ΔG) is effective for the lead-optimization process, binding ΔG s of 7-azaindole derivatives to the ATP binding site of glycogen synthase kinase-3 β (GSK-3 β) were calculated. The result was a significant correlation coefficient of $r = 0.895$ between calculated and observed ΔG s. This indicates that calculated ΔG reflects the inhibitory activities of 7-azaindole derivatives.

Pharmacophore Modeling, Virtual Screening, and in Vitro Testing Reveal Haloperidol, Eprazinone, and Fenbutrazate as Neurokinin Receptors Ligands

Yvonne Krautscheid, Carl Johann Åke Senning, Simone B. Sartori, Nicolas Singewald, Daniela Schuster [University of Innsbruck and Center for Molecular Biosciences Innsbruck (CMBI)], Hermann Stuppner

J.Chem. Infor. and Mod. **54**, 1747–1757, 2014.

Neurokinin receptors (NKR) have been shown to be involved in many physiological processes, rendering them promising novel drug targets, but also making them the possible cause for side effects of several drugs. Aiming to answer the question whether the binding to NKR could have a share in the side effects or even the desired effects of already licensed drugs, we generated a set of ligand-based common feature pharmacophore models based on the structural information about subtype-selective and nonselective NKR antagonists and screened an in-house database mainly composed of licensed drugs.

Medicinal Chemistry and Drug Design (Cont'd)

Dual Histamine H3R/Serotonin 5-HT4R Ligands with Antiamnesic Properties: Pharmacophore-Based Virtual Screening and Polypharmacology

Alban Lepailleur[Normandie Université], Thomas Freret, Stéphane Lemaître, Michel Boulouard, François Dauphin, Antoine Hinschberger, Fabienne Dulin, Aurélien Lesnard, Ronan Bureau, Sylvain Rault

J.Chem. Infor. and Mod. **54**, 1773–1784, 2014.

In recent years, preclinical and clinical studies have generated considerable interest in the development of histamine H3 receptor (H3R) antagonists as novel treatment for degenerative disorders associated with impaired cholinergic function. To identify novel scaffolds for H3R antagonism, a common feature-based pharmacophore model was developed and used to screen the 17,194 compounds of the CERMN (Centre d'Etudes et de Recherche sur le Médicament de Normandie) chemical library. Out of 268 virtual hits which have been gathered in 34 clusters, we were particularly interested in tricyclic derivatives also exhibiting a potent 5HT4R affinity.

In Silico Identification and Biological Evaluation of Novel Selective Serum/Glucocorticoid-Inducible Kinase 1 Inhibitors Based on the Pyrazolo-Pyrimidine Scaffold

Francesco Ortuso[University "Magna Græcia" of Catanzaro], Rosario Amato, Anna Artese, Lucia D'antona, Giosuè Costa, Cristina Talarico, Francesco Gigliotti, Cataldo Bianco, Francesco Trapasso, Silvia Schenone, Francesca Musumeci, Lorenzo Botta, Nicola Perrotti, Stefano Alcaro

J.Chem. Infor. and Mod. **54**, 1828–1832, 2014.

The serum/glucocorticoid-inducible kinase 1 (Sgk1) has demonstrated antiapoptotic function and the capability to regulate cell survival, proliferation, and differentiation. A pivotal role of Sgk1 in carcinogenesis and in resistance to anticancer therapy has been suggested. With the aim of identifying new Sgk1 modulators, 322 pyrazolo-pyrimidine derivatives have been virtually screened with respect to a crystallographic model of Sgk1. The top five ranked compounds have been evaluated demonstrating Sgk1 inhibition in vitro and selectivity compared to RAC-alpha serine/threonine-protein kinase (Akt1).

Dual-inhibitors of STAT5 and STAT3: studies from molecular docking and molecular dynamics simulations

Shengjuan Shao, Rilei Yu, Yanqing Yu, Yanni Li[Tianjin University]

J. Mol.Mod., **20**, 2399, 2014.

Although molecularly targeted therapy with imatinib has improved treatments of chronic myeloid leukemia (CML), clinical resistance gradually develops in patients with accelerated or blast phase CML. The inability of imatinib to cure CML suggests that inactivation of BCR-ABL kinase activity alone is not sufficient to control the disease. Here, molecular docking and molecular dynamics simulations were used to investigate the interactions of the drugs targeting STAT3 and STAT5 receptors at molecular level.

Homology modelling, docking, pharmacophore and site directed mutagenesis analysis to identify the critical amino acid residue of PknI from Mycobacterium tuberculosis

Srinivasan Kandasamy, Sameer Hassan, Radha Gopalaswamy, Sujatha Narayanan[National Institute for Research in Tuberculosis (NIRT) (ICMR)]

J. Mol.Graph. and Mod., **52**, 11-19 2014.

Tuberculosis is caused by Mycobacterium tuberculosis, an intracellular pathogen. PknI is one of the 11 functional Serine/Threonine Protein Kinases which is predicted to regulate the cell division of M. tuberculosis. In order to find newer drugs and vaccine we need to understand the pathogenesis of the disease. We have used the bioinformatics approach to identify the functionally active residues of PknI and to confirm the same with wet lab experiments. In the current study, we have created homology model for PknI and have done comparative structural analysis of PknI with other kinases.

Quantitative Structure-Activity Relations

Challenging the gold standard for 3D-QSAR: template CoMFA versus X-ray alignment

Bernd Wend [Certara, Martin-Kollar-Str. 17]t, Richard D. Cramer

J. Comp. Aided. Mol. Design, **28**, 803-824, 2014.

X-ray-based alignments of bioactive compounds are commonly used to correlate structural changes with changes in potencies, ultimately leading to three-dimensional quantitative structure–activity relationships such as CoMFA or CoMSIA models that can provide further guidance for the design of new compounds. We developed CoMFA and CoMSIA models from these X-ray-determined receptor-bound conformations and compared the results with models generated from ligand-centric Template CoMFA, finding that the fluctuations in the positions and conformations of compounds dominate X-ray-based alignments can yield poorer predictions than those from the self-consistent template CoMFA alignments.

Structural Similarity Based Kriging for Quantitative Structure Activity and Property Relationship Modeling

Ana L. Teixeira, Andre O. Falcao [University of Lisbon]

J.Chem. Infor. and Mod. **54**, 1833–1849, 2014.

Structurally similar molecules tend to have similar properties, i.e. closer molecules in the molecular space are more likely to yield similar property values while distant molecules are more likely to yield different values. Based on this principle, we propose the use of a new method that takes into account the high dimensionality of the molecular space, predicting chemical, physical, or biological properties based on the most similar compounds with measured properties. This methodology uses ordinary kriging coupled with three different molecular similarity approaches (based on molecular descriptors, fingerprints, and atom matching) which creates an interpolation map over the molecular space that is capable of predicting properties/activities for diverse chemical data sets.

Elucidating the structural basis of diphenyl ether derivatives as highly potent enoyl-ACP reductase inhibitors through molecular dynamics simulations and 3D-QSAR study

Pharit Kamsri, Auradee Punkvang, Patchareenart Saparpakorn, Supa Hannongbua, Stephan Irle, Pornpan Pungpo[Ubon Ratchathani University]

J. Mol.Mod., **20**, 2319, 2014.

Diphenyl ether derivatives are good candidates for anti-tuberculosis agents that display a promising potency for inhibition of InhA, an essential enoyl-acyl carrier protein (ACP) reductase involved in fatty acid biosynthesis pathways in *Mycobacterium tuberculosis*. In this work, key structural features for the inhibition were identified by 3D-QSAR CoMSIA models, constructed based on available experimental binding properties of diphenyl ether inhibitors, and a set of four representative compounds was subjected to MD simulations of inhibitor-InhA complexes for the calculation of binding free energies.

Carbon Nanoparticles

Tailoring Pull-out Properties of Single-Walled Carbon Nanotube Bundles by Varying Binding Structures through Molecular Dynamics Simulation

Liuyang Zhang , Xianqiao Wang [University of Georgia]

J. Chem. Theor. and Comp, **10**, 3200–3206, 2014.

Single-walled carbon nanotubes (SWCNTs) have demonstrated a remarkable capacity for self-assembly into nanobundles through intermolecular van der Waals interactions, bestowing these agglomerates extraordinary mechanical, thermal, and electrical properties. By utilizing molecular dynamics simulation, here we present the construction of SWCNT bundles with discrete cylindrical and continuous helical binders by noncovalent coating of the bundle surface with sp²-hybridized carbon networks.

1.2. Biopolymers

Bioinformatics and Cheminformatics

The Bio-Community Perl toolkit for microbial ecology

Florent E. Angly [The University of Queensland, Brisbane St Lucia], Christopher J. Fields, Gene W. Tyson

Bioinformatics. **30**, 1926-1927, 2014.

The development of bioinformatic solutions for microbial ecology in Perl is limited by the lack of modules to represent and manipulate microbial community profiles from amplicon and meta-omics studies. Here we introduce Bio-Community, an open-source, collaborative toolkit that extends BioPerl. Bio-Community interfaces with commonly used programs using various file formats, including BIOM, and provides operations such as rarefaction and taxonomic summaries.

Orione, a web-based framework for NGS analysis in microbiology

Gianmauro Cuccuru [CRS4, Science and Technology Park Polaris], Massimiliano Orsini, Andrea Pinna, Andrea Sbardellati, Nicola Soranzo, Antonella Travaglione, Paolo Uva, Gianluigi Zanetti, Giorgio Fotia

Bioinformatics. **30**, 1928-1929, 2014.

End-to-end next-generation sequencing microbiology data analysis requires a diversity of tools covering bacterial resequencing, *de novo* assembly, scaffolding, bacterial RNA-Seq, gene annotation and metagenomics. However, the construction of computational pipelines that use different software packages is difficult owing to a lack of interoperability, reproducibility and transparency. To overcome these limitations we present Orione, a Galaxy-based framework consisting of publicly available research software and specifically designed pipelines to build complex, reproducible workflows for next-generation sequencing microbiology data analysis.

pRESTO: a toolkit for processing high-throughput sequencing raw reads of lymphocyte receptor repertoires

Jason A. Vander Heiden, Gur Yaari, Mohamed Uduman, Joel N.H. Stern, Kevin C. O'Connor, David A. Hafler, Francois Vigneault, Steven H. Kleinstein[Yale University]

Bioinformatics. **30**, 1930-1932, 2014.

Driven by dramatic technological improvements, large-scale characterization of lymphocyte receptor repertoires via high-throughput sequencing is now feasible. Although promising, the high germline and somatic diversity, especially of B-cell immunoglobulin repertoires, presents challenges for analysis requiring the development of specialized computational pipelines. We developed the REpertoire Sequencing Toolkit (pRESTO) for processing reads from high-throughput lymphocyte receptor studies.

Bioinformatics and Cheminformatics (Cont'd)

Genome-wide quantitative analysis of DNA methylation from bisulfite sequencing data

Kemal Akman [Max Planck Institute for Plant Breeding Research], Thomas Haaf, Silvia Gravina, Jan Vijg, Achim Tresch

Bioinformatics. **30**, 1933-1934, 2014.

Here we present the open-source R/Bioconductor software package BEAT (BS-Seq Epimutation Analysis Toolkit). It implements all bioinformatics steps required for the quantitative high-resolution analysis of DNA methylation patterns from bisulfite sequencing data, including the detection of regional epimutation events, i.e. loss or gain of DNA methylation at CG positions relative to a reference.

Zebra: a web server for bioinformatic analysis of diverse protein families

Dmitry Suplatov, Evgeny Kirilin, Vakil Takhaviev, Vytas Švedas [Lomonosov Moscow State University]

J. Biomol. Stru. and Dyn., **32**, 1752-1758, 2014.

During evolution of proteins from a common ancestor, one functional property can be preserved while others can vary leading to functional diversity. A systematic study of the corresponding adaptive mutations provides a key to one of the most challenging problems of modern structural biology – understanding the impact of amino acid substitutions on protein function. This paper describes Zebra web server – a powerful remote platform that implements a novel bioinformatic analysis algorithm to study diverse protein families.

iBIOMES Lite: Summarizing Biomolecular Simulation Data in Limited Settings

Julien C. Thibault, Thomas E. Cheatham, III [University of Utah], and Julio C. Facelli

J.Chem. Infor. and Mod. **54**, 1810–1819, 2014.

As the amount of data generated by biomolecular simulations dramatically increases, new tools need to be developed to help manage this data at the individual investigator or small research group level. In this paper, we introduce iBIOMES Lite, a lightweight tool for biomolecular simulation data indexing and summarization. The main goal of iBIOMES Lite is to provide a simple interface to summarize computational experiments in a setting where the user might have limited privileges and limited access to IT resources.

Protein Sequence Analysis and Alignment

The design of a peptide sequence to inhibit HIV replication: a search algorithm combining Monte Carlo and self-consistent mean field techniques

Xingqing Xiao, Carol K. Hall [North Carolina State University], Paul F. Agris

J. Biomol. Stru. and Dyn., **32**, 1523-1536, 2014.

We developed a search algorithm combining Monte Carlo (MC) and self-consistent mean field techniques to evolve a peptide sequence that has good binding capability to the anticodon stem and loop (ASL) of human lysine tRNA species, tRNA^{Lys3}, with the ultimate purpose of breaking the replication cycle of human immunodeficiency virus-1. The starting point is the 15-amino-acid sequence, RVTHHAFLGAHRTVG, found experimentally by Agris and co-workers to bind selectively to hypermodified tRNA^{Lys3}. The peptide backbone conformation is determined via atomistic simulation of the peptide-ASL^{Lys3} complex and then held fixed throughout the search.

Protein Secondary Structure

Comparing atomistic molecular mechanics force fields for a difficult target: a case study on the Alzheimer's amyloid β -peptide

Stacey R. Gerben, Justin A. Lemkul, Anne M. Brown, David R. Bevan [Department of Biochemistry, Virginia Tech]

J. Biomol. Stru. and Dyn., 32, 1817-1832, 2014.

Macromolecular function arises from structure, and many diseases are associated with misfolding of proteins. Molecular simulation methods can augment experimental techniques to understand misfolding and aggregation pathways with atomistic resolution, but the reliability of these predictions is a function of the parameters used for the simulation. There are many biomolecular force fields available, but most are validated using stably folded structures. Here, we present the results of molecular dynamics simulations on the intrinsically disordered amyloid β -peptide ($A\beta$), whose misfolding and aggregation give rise to the symptoms of Alzheimer's disease.

Transformation between α -helix and β -sheet structures of one and two polyglutamine peptides in explicit water molecules by replica-exchange molecular dynamics simulations

Hsin-Lin Chiang, Chun-Jung Chen, Hisashi Okumura, Chin-Kun Hu [Academia Sinica]

J. Comp. Chem., 35, 1430–1437, 2014.

Aggregation of polyglutamine peptides with β -sheet structures is related to some important neurodegenerative diseases such as Huntington's disease. However, it is not clear how polyglutamine peptides form the β -sheets and aggregate. To understand this problem, we performed all-atom replica-exchange molecular dynamics simulations of one and two polyglutamine peptides with 10 glutamine residues in explicit water molecules.

Protein Secondary Structure Classification Revisited: Processing DSSP Information with PSSC

Jan Zacharias, Ernst-Walter Knapp [Freie Universität Berlin]

J. Chem. Infor. and Mod. 54, 2166–2179, 2014.

A first step toward three-dimensional protein structure description is the characterization of secondary structure. The most widely used program for secondary structure assignment remains DSSP, introduced in 1983, with currently more than 400 citations per year. DSSP output is in a one-letter representation, where much of the information on DSSP's internal description is lost. Recently it became evident that DSSP overlooks most π -helical structures, which are more prevalent and important than anticipated before. We introduce an alternative concept, representing the internal structure characterization of DSSP as an eight-character string that is human-interpretable and easy to parse by software.

Detailed Microscopic Unfolding Pathways of an α -Helix and a β -Hairpin: Direct Observation and Molecular Dynamics

Gouri S. Jas, Wendy A. Hegefeld, C. Russell Middaugh, Carey K. Johnson, Krzysztof Kuczerka [University of Kansas]

J. Phys. Chem. B., 118, 7233–7246, 2014.

We present a combined experimental and computational study of unfolding pathways of a model 21-residue α -helical heteropeptide (W1H5-21) and a 16-residue β -hairpin (GB41–56). Experimentally, we measured fluorescence energy transfer efficiency as a function of temperature, employing natural tryptophans as donors and dansylated lysines as acceptors. Secondary structural analysis was performed with circular dichroism and Fourier transform infrared spectroscopy. Our studies present markedly different unfolding pathways of the two elementary secondary structural elements.

Protein Secondary Structure (Cont'd)

Combining Classical MD and QM Calculations to Elucidate Complex System Nucleation: A Twisted, Three-Stranded, Parallel β -Sheet Seeds Amyloid Fibril Conception

Miguel Mompeán, Carlos González, Enrique Lomba, Douglas V. Laurents [Instituto de Química Física “Rocasolano”]

J. Phys. Chem. B., **118**, 7312–7316, 2014.

The crystal structure of the Sup35 prion segment, GNNQQNY, revealed precise side chain packing and an extensive H-bond network. However, the conformers and stabilizing interactions involved at nascent amyloid formation are still unclear. Here, long molecular dynamics simulations and quantum mechanical calculations have been utilized to study the conformation and energetics of the initial structure that acts to nucleate further growth. Considering all the plausible intermediates that may act as stepping stones, we find that the initial nucleus is a twisted single-layer, three-stranded parallel β -sheet.

Comparative or Homology Modeling

Preventing the return of smallpox: molecular modeling studies on thymidylate kinase from *Variola virus*

Ana Paula Guimarães, Teodorico Castro Ramalho, Tanos Celmar Costa França [Military Institute of Engineering]

J. Biomol. Stru. and Dyn., **32**, 1601-1612, 2014.

Smallpox was one of the most devastating diseases in the human history and still represents a serious menace today due to its potential use by bioterrorists. Considering this threat and the non-existence of effective chemotherapy, we propose the enzyme thymidylate kinase from *Variola virus* (VarTMPK) as a potential target to the drug design against smallpox. We first built a homology model for VarTMPK and performed molecular docking studies on it in order to investigate the interactions with inhibitors of *Vaccinia virus* TMPK (VacTMPK).

New insight in the structural features of haloadaptation in α -amylases from halophilic *Archaea* following homology modeling strategy: folded and stable conformation maintained through low hydrophobicity and highly negative charged surface

Mohamed Amine Zorgani [Université François Rabelais de Tours], Kevin Patron, Mickaël Desvaux

J. Comp. Aided. Mol. Design, **28**, 721-734, 2014.

Proteins from halophilic archaea, which live in extreme saline conditions, have evolved to remain folded, active and stable at very high ionic strengths. Understanding the mechanism of haloadaptation is the first step toward engineering of halostable biomolecules. Amylases are one of the main enzymes used in industry. Yet, no three-dimensional structure has been experimentally resolved for α -amylases from halophilic archaea. In this study, homology structure modeling of α -amylases from the halophilic archaea *Haloarcula marismortui*, *Haloarcula hispanica*, and *Halalkalicoccus jeotgali* were performed

Induced fit docking, pharmacophore modeling, and molecular dynamic simulations on thiazolidinedione derivatives to explore key interactions with Tyr48 in polyol pathway

Manga Vijjulatha [Osmania University], Yamini Lingala, RaviRaja Tejaswi Merugu

J. Mol.Mod., **20**, 2348, 2014.

To obtain a scientific thought and expedition to explore key interactions with Tyr48 in aldose reductase (ALR), combined study of pharmacophore modeling, induced fit docking, and dynamics studies were performed on ALR. A stereo chemically and energetically valid model of ALR-NADP⁺ complex was developed using homology modeling technique. Statistically a significant five point pharmacophore model was designed on a set of 54 thiazolidinedione derivatives with good external and internal predictive ability.

Protein Conformational Analysis

A Rotamer Library to Enable Modeling and Design of Peptoid Foldamers

P. Douglas Renfrew, Timothy W. Craven, Glenn L. Butterfoss, Kent Kirshenbaum, Richard Bonneau [New York University]

J. Am. Chem. Soc., 2013, **136**, 8772–8782, 2014.

Peptoids are a family of synthetic oligomers composed of N-substituted glycine units. Along with other “foldamer” systems, peptoid oligomer sequences can be predictably designed to form a variety of stable secondary structures. We introduce a computational approach to provide accurate conformational and energetic parameters for peptoid side chains needed for successful modeling and design. We find that peptoids can be described by a “rotamer” treatment, similar to that established for proteins, in which the peptoid side chains display rotational isomerism to populate discrete regions of the conformational landscape.

Metal-Induced Conformational Changes of Human Metallothionein-2A: A Combined Theoretical and Experimental Study of Metal-Free and Partially Metalated Intermediates

Shu-Hua Chen, Liuxi Chen, David H. Russell [Texas A&M University]

J. Am. Chem. Soc., 2013, **136**, 9499–9508, 2014.

Electrospray ionization ion mobility mass spectrometry (ESI IM-MS) and molecular dynamics (MD) simulations reveal new insights into metal-induced conformational changes and the mechanism for metalation of human metallothionein-2A (MT), an intrinsically disordered protein. ESI of solutions containing apoMT yields multiple charge states of apoMT; following addition of Cd²⁺ to the solution, ESI yields a range of CdiMT (*i* = 1–7) product ions (see Chen et al. *Anal. Chem.* 2013, **85**, 7826–33). Ion mobility arrival-time distributions (ATDs) for the CdiMT (*i* = 0–7) ions reveal a diverse population of ion conformations.

Multi-State, Allosterically-Regulated Molecular Receptor With Switchable Selectivity

Jose Mendez-Arroyo, Joaquín Barroso-Flores, Alejo M. Lifschitz, Amy A. Sarjeant, Charlotte L. Stern, Chad A. Mirkin [Northwestern University]

J. Am. Chem. Soc., 2013, **136**, 10340–10348, 2014.

A biomimetic, ion-regulated molecular receptor was synthesized via the Weak-Link Approach (WLA). This structure features both a calix[4]arene moiety which serves as a molecular recognition unit and an activity regulator composed of hemilabile phosphine alkyl thioether ligands (P,S) chelated to a Pt(II) center. The environment at the regulatory site dictates the charge and the structural conformation of the entire assembly resulting in three accessible binding configurations: one closed, inactive state and two open, active states.

Full length amylin oligomer aggregation: insights from molecular dynamics simulations and implications for design of aggregation inhibitors

Workalemahu Mikre Berhanu, Artëm E. Masunov [University of Central Florida]

J. Biomol. Stru. and Dyn., 32, 1651-1669, 2014.

Amyloid oligomers are considered to play essential roles in the pathogenesis of amyloid-related degenerative diseases including type 2 diabetes. Using an explicit solvent all atomic MD simulation, we explored the stability, conformational dynamics and association force of different single-layer models of the full-length wild-type and glycine mutants of amylin (pentamer) obtained from a recent high resolution fibril model. The RMSF profile shows enhanced flexibility in the disorder (Lys1-Cys7) and turn region (Ser19-Gly23), along with smallest fluctuation at the residues (Asn14-Phe15-Leu16-Val17-His18) of β_1 region and (Ala25-Ile26-Leu27-Ser28-Ser29) of the β_2 region.

Protein Conformational Analysis (Cont'd)

***Plasmodium falciparum* Hsp70-x: a heat shock protein at the host-parasite interface**

Rowan Hatherley, Gregory L. Blatch , Özlem Tasthan Bishop[Sabancı University]

J. Biomol. Stru. and Dyn., 32, 1766-1779, 2014.

Plasmodium falciparum 70 kDa heat shock proteins (PfHsp70s) are expressed at all stages of the pathogenic erythrocytic phase of the malaria parasite life cycle. There are six PfHsp70s, all of which have orthologues in other plasmodial species, except for PfHsp70-x which is unique to *P. falciparum*. This research highlights a number of original results obtained by a detailed bioinformatics analysis of the protein. Large-scale sequence analysis indicated the presence of an extended transit peptide sequence of PfHsp70-x which potentially directs it to the endoplasmic reticulum (ER).

Pairwise decomposition of an MMGBSA energy function for computational protein design

Thomas Gaillard , Thomas Simonson[Laboratoire de Biochimie (CNRS UMR7654)]

J. Comp. Chem., 35, 1371–1387, 2014.

Computational protein design (CPD) aims at predicting new proteins or modifying existing ones. The computational challenge is huge as it requires exploring an enormous sequence and conformation space. The difficulty can be reduced by considering a fixed backbone and a discrete set of sidechain conformations. Another common strategy consists in precalculating a pairwise energy matrix, from which the energy of any sequence/conformation can be quickly obtained. In this work, we examine the pairwise decomposition of protein MMGBSA energy functions from a general theoretical perspective, and an implementation proposed earlier for CPD.

Enrichment of Chemical Libraries Docked to Protein Conformational Ensembles and Application to Aldehyde Dehydrogenase 2

Bo Wang, Cameron D. Buchman, Liwei Li, Thomas D. Hurley, Samy O. Meroueh[Indiana University School of Medicine]

J.Chem. Infor. and Mod. 54, 2105–2116, 2014.

Molecular recognition is a complex process that involves a large ensemble of structures of the receptor and ligand. Yet, most structure-based virtual screening is carried out on a single structure typically from X-ray crystallography. Explicit-solvent MD simulations offer an opportunity to sample multiple conformational states of a protein. Here we evaluate our recently developed scoring method SVMSP in its ability to enrich chemical libraries docked to MD structures of seven proteins from the Directory of Useful Decoys (DUD).

Assessing the Accuracy of Two Enhanced Sampling Methods Using EGFR Kinase Transition Pathways: The Influence of Collective Variable Choice

Albert C. Pan, Thomas M. Weinreich, Yibing Shan, Daniele P. Scarpazza, David E. Shaw[New York]

J. Chem. Theor. and Comp., 10, 2860–2865, 2014.

Structurally elucidating transition pathways between protein conformations gives deep mechanistic insight into protein behavior but is typically difficult. Unbiased molecular dynamics (MD) simulations provide one solution, but their computational expense is often prohibitive, motivating the development of enhanced sampling methods that accelerate conformational changes in a given direction, embodied in a collective variable. The accuracy of such methods is unclear for complex protein transitions, because obtaining unbiased MD data for comparison is difficult.

Protein Conformational Analysis (Cont'd)

Computational Recipe for Efficient Description of Large-Scale Conformational Changes in Biomolecular Systems

Mahmoud Moradi , Emad Tajkhorshid [University of Illinois at Urbana–Champaign]

J. Chem. Theor. and Comp, **10**, 2866–2880, 2014.

Characterizing large-scale structural transitions in biomolecular systems poses major technical challenges to both experimental and computational approaches. On the computational side, efficient sampling of the configuration space along the transition pathway remains the most daunting challenge. Recognizing this issue, we introduce a knowledge-based computational approach toward describing large-scale conformational transitions using (i) nonequilibrium, driven simulations combined with work measurements and (ii) free energy calculations using empirically optimized biasing protocols.

A Newfound Cancer-Activating Mutation Reshapes the Energy Landscape of Estrogen-Binding Domain

Wei Huang, Krishnakumar M. Ravikumar, Sichun Yang [Case Western Reserve University]

J. Chem. Theor. and Comp, **10**, 2897–2900, 2014.

The ligand-binding domain (LBD) of an estrogen receptor undergoes a large conformational switching from an inactive to active state in response to hormone stimuli. Very recently, a novel D538G mutant has been identified to be active in advanced breast cancer tumors. Here, we ask if molecular simulations can provide insight on its mechanistic impact on the receptor's activation status. It has been challenging for ab initio modeling to identify two distinct conformations of a single amino acid sequence as large as that of the LBD.

Conformational Transition Pathways of Epidermal Growth Factor Receptor Kinase Domain from Multiple Molecular Dynamics Simulations and Bayesian Clustering

Yan Li, Xiang Li, Weiya Ma, Zigang Dong [University of Minnesota]

J. Chem. Theor. and Comp, **10**, 3503–3511, 2014.

The epidermal growth factor receptor (EGFR) is aberrantly activated in various cancer cells and an important target for cancer treatment. Deep understanding of EGFR conformational changes between the active and inactive states is of pharmaceutical interest. Here we present a strategy combining multiply targeted molecular dynamics simulations, unbiased molecular dynamics simulations, and Bayesian clustering to investigate transition pathways during the activation/inactivation process of EGFR kinase domain.

Correlation as a Determinant of Configurational Entropy in Supramolecular and Protein Systems

Andrew T. Fenley, Benjamin J. Killian, Vladimir Hnizdo, Adam Fedorowicz, Dan S. Sharp, Michael K. Gilson [University of California at San Diego]

J. Phys. Chem. B., **118**, 6447–6455, 2014.

For biomolecules in solution, changes in configurational entropy are thought to contribute substantially to the free energies of processes like binding and conformational change. In principle, the configurational entropy can be strongly affected by pairwise and higher-order correlations among conformational degrees of freedom. However, the literature offers mixed perspectives regarding the contributions that changes in correlations make to changes in configurational entropy for such processes. Here we take advantage of powerful techniques for simulation and entropy analysis to carry out rigorous in silico studies of correlation in binding and conformational changes.

Protein Conformational Analysis (Cont'd)

Insight into HIV-1 reverse transcriptase–aptamer interaction from molecular dynamics simulations

Niran Aeksiri, Napat Songtawee, M. Paul Gleeson, Supa Hannongbua, Kiattawee Choowongkomon [Kasetsart University]

J. Mol.Mod., **20**, 2380, 2014.

Human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT) is considered to be one of the key targets for antiviral drug therapy. The emergence of the aptamers as potential inhibitors against HIV-1 reverse transcriptase has attracted the attention of the scientific community because these macromolecules can effectively inhibit HIV-1 RT with between micromolar to picomolar concentrations. We have employed three separate models: apo HIV-1 RT, HIV-1 RT with a bound RNA aptamer, and HIV-1 RT with a bound DNA substrate. The results show that HIV-1 RT complex with an aptamer was more stable than that with DNA substrate.

Protein Structure Analysis

Statistical Mechanics of the Denatured State of a Protein Using Replica-Averaged Metadynamics

Carlo Camilloni, Michele Vendruscolo [University of Cambridge]

J. Am. Chem. Soc., 2013, **136**, 8982–8991, 2014.

The characterization of denatured states of proteins is challenging because the lack of permanent structure in these states makes it difficult to apply to them standard methods of structural biology. In this work we use all-atom replica-averaged metadynamics (RAM) simulations with NMR chemical shift restraints to determine an ensemble of structures representing an acid-denatured state of the 86-residue protein ACBP.

Facing the Challenges of Structure-Based Target Prediction by Inverse Virtual Screening

Karen T. Schomburg, Stefan Bietz, Hans Briem, Angela M. Henzler, Sascha Urbaczek, Matthias Rarey [University of Hamburg]

J.Chem. Infor. and Mod. **54**, 1676–1686, 2014.

Computational target prediction for bioactive compounds is a promising field in assessing off-target effects. Structure-based methods not only predict off-targets, but, simultaneously, binding modes, which are essential for understanding the mode of action and rationally designing selective compounds. Here, we highlight the current open challenges of computational target prediction methods based on protein structures and show why inverse screening rather than sequential pairwise protein–ligand docking methods are needed. A new inverse screening method based on triangle descriptors is introduced: iRAISE (inverse RapidIndex-based Screening Engine).

Structure and Dynamics Analysis on Plexin-B1 Rho GTPase Binding Domain as a Monomer and Dimer

Liqun Zhang [Medical School of Case Western Reserve University], Thomas Centa, Matthias Buck

J. Phys. Chem. B., **118**, 7302–7311, 2014.

Plexin-B1 is a single-pass transmembrane receptor. Its Rho GTPase binding domain (RBD) can associate with small Rho GTPases and can also self-bind to form a dimer. In total, more than 400 ns of NAMD molecular dynamics simulations were performed on RBD monomer and dimer. Different analysis methods, such as root mean squared fluctuation (RMSF), order parameters (S²), dihedral angle correlation, transfer entropy, principal component analysis, and dynamical network analysis, were carried out to characterize the motions seen in the trajectories. RMSF results show that after binding, the L4 loop becomes more rigid, but the L2 loop and a number of residues in other regions become slightly more flexible.

Protein Structure Analysis (Cont'd)

3D Flexible Alignment Using 2D Maximum Common Substructure: Dependence of Prediction Accuracy on Target-Reference Chemical Similarity

Takeshi Kawabata[Osaka University], Haruki Nakamura

J.Chem. Infor. and Mod. **54**, 1850–1863, 2014.

A protein-bound conformation of a target molecule can be predicted by aligning the target molecule on the reference molecule obtained from the 3D structure of the compound–protein complex. This strategy is called “similarity-based docking”. For this purpose, we develop the flexible alignment program fkcombu, which aligns the target molecule based on atomic correspondences with the reference molecule. The correspondences are obtained by the maximum common substructure (MCS) of 2D chemical structures, using our program kcombu.

Automated Building of Organometallic Complexes from 3D Fragments

Marco Foscato, Vishwesh Venkatraman, Giovanni Occhipinti, Bjørn K. Alsberg, Vidar R. Jensen [University of Bergen]

J.Chem. Infor. and Mod. **54**, 1919–1931, 2014.

A method for the automated construction of three-dimensional (3D) molecular models of organometallic species in design studies is described. Molecular structure fragments derived from crystallographic structures and accurate molecular-level calculations are used as 3D building blocks in the construction of multiple molecular models of analogous compounds. The method allows for precise control of stereochemistry and geometrical features that may otherwise be very challenging, or even impossible, to achieve with commonly available generators of 3D chemical structures.

Dynamic Structure of NGF and proNGF Complexed with p75NTR: Pro-Peptide Effect

A. C. Pimenta, D. F. A. R. Dourado, J. M. Martins, A. Melo, M. N. Dias Soeiro Cordeiro, R. D. Almeida, G. Morra, I. S. Moreira [Faculdade de Ciências da Universidade do Porto]

J.Chem. Infor. and Mod. **54**, 2051–2067, 2014.

Crystallographic structures of NGF/p75NTR and proNGF/p75NTR were previously obtained in 2:1 and 2:2 stoichiometries, respectively. However, evidence shows that both stoichiometries can occur for mature neurotrophins and pro-neurotrophins. We used Molecular Dynamics (MD) simulations to examine the energetic and structural characteristics of these two complete systems as well as the uncomplexed forms of NGF and understand how these could translate in a new view of different biological outcomes.

Effect of Taiwan Mutation (D7H) on Structures of Amyloid- β Peptides: Replica Exchange Molecular Dynamics Study

Phan Minh Truong, Man Hoang Viet, Phuong H. Nguyen, Chin-Kun Hu, Mai Suan Li [Polish Academy of Sciences]

J. Phys. Chem. B., **118**, 8972–8981, 2014.

Recent experiments have shown that the Taiwan mutation (D7H) slows the fibril formation of amyloid peptides A β 40 and A β 42. Motivated by this finding, we have studied the influence of D7H mutation on structures of A β peptide monomers using the replica exchange molecular dynamics simulations with OPLS force field and implicit water model. Our study reveals that the mechanism behind modulation of aggregation rates is associated with decrease of β -content and dynamics of the salt bridge D23–K28.

Protein Dynamics

Motifs tree: a new method for predicting post-translational modifications

Christophe Charpillot, Anne-Lise Veuthey, Bastien Chopard, Jean-Luc Falcone [University of Geneva]

Bioinformatics. **30**, 1974-1982, 2014.

Post-translational modifications (PTMs) are important steps in the maturation of proteins. Several models exist to predict specific PTMs, from manually detected patterns to machine learning methods. On one hand, the manual detection of patterns does not provide the most efficient classifiers and requires an important workload, and on the other hand, models built by machine learning methods are hard to interpret and do not increase biological knowledge. Therefore, we developed a novel method based on patterns discovery and decision trees to predict PTMs.

Hidden Regularity and Universal Classification of Fast Side Chain Motions in Proteins

Rajitha Rajeshwar T., Jeremy C. Smith, Marimuthu Krishnan [International Institute of Information Technology, Gachibowli]

J. Am. Chem. Soc., 2013, **136**, 8590–8605, 2014.

Proteins display characteristic dynamical signatures that appear to be universal across all proteins regardless of topology and size. Here, we systematically characterize the universal features of fast side chain motions in proteins by examining the conformational energy surfaces of individual residues obtained using enhanced sampling molecular dynamics simulation. The side chain conformational free energy surfaces obtained using the adaptive biasing force (ABF) method for a set of eight proteins with different molecular weights and secondary structures are used to determine the methyl axial NMR order parameters (O_{ax}^2), populations of side chain rotamer states (ρ), conformational entropies (S_{conf}), probability fluxes, and activation energies for side chain inter-rotameric transitions.

α -Synuclein-Induced Membrane Remodeling Is Driven by Binding Affinity, Partition Depth, and Interleaflet Order Asymmetry

Anthony R. Braun, Michael M. Lacy, Vanessa C. Ducas, Elizabeth Rhoades, Jonathan N. Sachs [University of Minnesota]

J. Am. Chem. Soc., 2013, **136**, 9962–9972, 2014.

We have investigated the membrane remodeling capacity of the N-terminal membrane-binding domain of α -synuclein (α -Syn100). Using fluorescence correlation spectroscopy and vesicle clearance assays, we show that α -Syn100 fully tubulates POPG vesicles, the first demonstration that the amphipathic helix on its own is capable of this effect. We also show that at equal density of membrane-bound protein, α -Syn has dramatically reduced affinity for, and does not tubulate, vesicles composed of a 1:1 POPG:POPC mixture. Coarse-grained molecular dynamics simulations suggested that the difference between the p

The pH dependence of flavivirus envelope protein structure: insights from molecular dynamics simulations

Carlos Alessandro Fuzo [Universidade de São Paulo], Léo Degreève

J. Biomol. Stru. and Dyn., 32, 1563-1574, 2014.

We employed a low computational cost scheme to explore the behavior of the E protein by molecular dynamics (MD) simulations of complete systems that include the protein, the solvent, and ions. The procedure alternates cyclically the update of the ionization states of the protein residues with common MD steps applied to the new ionization configuration. Important pH-dependent protein structure rearrangements consistent with the changes of the protonation states of conserved histidine residues were observed.

Protein Dynamics (Cont'd)

A study of the structural properties and thermal stability of human Bcl-2 by molecular dynamics simulations

Ian Ilizaliturri-Flores, José Correa-Basurto, Claudia G. Benítez-Cardoza, Absalom Zamorano-Carrillo [Instituto Politécnico Nacional]

J. Biomol. Stru. and Dyn., 32, 1707-1719, 2014.

The anti-apoptotic B-cell lymphoma 2 (Bcl-2) protein interacts with several proteins that regulate the apoptotic properties of cells. In this research, we conduct several all-atom molecular dynamics (MD) simulations under high-temperature unfolding conditions, from 400 to 800 K, for 25 ns. These simulations were performed using a model of an engineered Bcl-2 human protein (Bcl-2- $\Delta 22\text{S}3$), which lacks 22 C-terminal residues of the transmembrane domain. The aim of this study is to gain insight into the structural behavior of Bcl-2- $\Delta 22\text{S}3$ by mapping the conformational movements involved in Bcl-2 stability and its biological function.

A comparison of the electromechanical properties of structurally diverse proteins by molecular dynamics simulation

Asmaa A.A. Elsheshiny, Alison E. Ashcroft, Sarah A. Harris [University of Leeds]

J. Biomol. Stru. and Dyn., 32, 1734-1741, 2014.

Proteins are subjected to electric fields both within the cell and during routine biochemical analysis. We have used atomistic molecular dynamics simulations to study conformational changes within three structurally diverse proteins subjected to high electric fields. At electric fields in excess of .5 V/nm, major structural changes were observed in all three proteins due to charge redistribution within the biomolecule. However, the electromechanical resilience was found to be highly dependent on the protein secondary structure, with α -helices showing a particularly high susceptibility to deformation by the applied electric field.

Insights on pH-dependent conformational changes of mosquito odorant binding proteins by molecular dynamics simulations

Malini Manoharan, Patrick F.J. Fuchs, Ramanathan Sowdhamini [Tata Institute for Fundamental Research], Bernard Offmann

J. Biomol. Stru. and Dyn., 32, 1742-1751, 2014.

Odorant binding proteins (OBPs) are the primary components of the insect olfactory mechanism and have been documented to play an important role in the host-seeking mechanism of mosquitoes. In this paper, the effect of pH on the conformational flexibility of mosquito OBPs is assessed computationally using molecular dynamics simulations of a mosquito OBP "CquiOBP1" bound to its pheromone 3OG (PDB ID: 3OGN). Conformational twist of a loop, driven by a set of well-characterized changes in intramolecular interactions of the loop, is demonstrated.

In silico concurrent multisite pH titration in proteins

Hao Hu [University of Hong Kong], Lin Shen

J. Comp. Chem., 35, 1491–1498, 2014.

The concurrent proton binding at multiple sites in macromolecules such as proteins and nucleic acids is an important yet challenging problem in biochemistry. We develop an efficient generalized Hamiltonian approach to attack this issue. Based on the previously developed generalized-ensemble methods, an effective potential energy is constructed which combines the contributions of all (relevant) protonation states of the molecule. The effective potential preserves important phase regions of all states and, thus, allows efficient sampling of these regions in one simulation.

Protein Dynamics (Cont'd)

A Possible Mechanism for Redox Control of Human Neuroglobin Activity

Alexander N. Morozov, James P. Roach, Margarita Kotzer, David C. Chatfield [Florida International University]

J. Chem. Infor. and Mod. **54**, 1997–2003, 2014.

Neuroglobin (Ngb) promotes neuron survival under hypoxic/ischemic conditions. In vivo and in vitro assays provide evidence for redox-regulated functioning of Ngb. On the basis of X-ray crystal structures and our MD simulations, a mechanism for redox control of human Ngb (hNgb) activity via the influence of the CD loop on the active site is proposed. We provide evidence that the CD loop undergoes a strand-to-helix transition when the external environment becomes sufficiently oxidizing, and that this CD loop conformational transition causes critical restructuring of the active site.

Application of Molecular-Dynamics Based Markov State Models to Functional Proteins

Robert D. Malmstrom, Christopher T. Lee, Adam T. Van Wart, Rommie E. Amaro [University of California San Diego]

J. Chem. Theor. and Comp. **10**, 2648–2657, 2014.

Owing to recent developments in computational algorithms and architectures, it is now computationally tractable to explore biologically relevant, equilibrium dynamics of realistically sized functional proteins using all-atom molecular dynamics simulations. Molecular dynamics simulations coupled with Markov state models is a nascent but rapidly growing technology that is enabling robust exploration of equilibrium dynamics. The objective of this work is to explore the challenges of coupling molecular dynamics simulations and Markov state models in the study of functional proteins.

Constant pH Molecular Dynamics in Explicit Solvent with Enveloping Distribution Sampling and Hamiltonian Exchange

Juyong Lee [National Institutes of Health, Bethesda], Benjamin T. Miller, Ana Damjanović, Bernard R. Brooks

J. Chem. Theor. and Comp. **10**, 2738–2750, 2014.

We present a new computational approach for constant pH simulations in explicit solvent based on the combination of the enveloping distribution sampling (EDS) and Hamiltonian replica exchange (HREX) methods. Unlike constant pH methods based on variable and continuous charge models, our method is based on discrete protonation states. EDS generates a hybrid Hamiltonian of different protonation states. A smoothness parameter s is used to control the heights of energy barriers of the hybrid-state energy landscape. A small s value facilitates state transitions by lowering energy barriers.

Thermodynamics of Deca-alanine Folding in Water

Anthony Hazel, Christophe Chipot, James C. Gumbart [Georgia Institute of Technology]

J. Chem. Theor. and Comp. **10**, 2836–2844, 2014.

The determination of the folding dynamics of polypeptides and proteins is critical in characterizing their functions in biological systems. Numerous computational models and methods have been developed for studying structure formation at the atomic level. Due to its small size and simple structure, deca-alanine is used as a model system in molecular dynamics (MD) simulations. The free energy of unfolding in vacuum has been studied extensively using the end-to-end distance of the peptide as the reaction coordinate. However, few studies have been conducted in the presence of explicit solvent.

Protein Dynamics (Cont'd)

Including the Dispersion Attraction into Structure-Adapted Fast Multipole Expansions for MD Simulations

Konstantin Lorenzen, Christoph Wichmann, Paul Tavan
[Ludwig-Maximilians-Universität]

J. Chem. Theor. and Comp., **10**, 3244–3259, 2014.

Molecular dynamics (MD) simulations of protein–solvent systems, which are modeled by polarizable or nonpolarizable all-atom force fields and are enclosed by periodic boundaries, require accurate and efficient algorithms for the computation of the long-range interactions. A possible choice is the fast structure-adapted multipole method called SAMMp/RF (Lorenzen et al. *J. Chem. Theory Comput.* 2012, 8, 3628–3636). Here, we substantially extend this method by adding q th order Taylor expansions of the dispersion attraction and by formulating an interaction acceptance criterion for cluster–cluster interactions, which is based on substance-specific accuracy estimates.

Interactions of a Water-Soluble Fullerene Derivative with Amyloid- β Protofibrils: Dynamics, Binding Mechanism, and the Resulting Salt-Bridge Disruption

Xiaoying Zhou, Wenhui Xi, Yin Luo, Siqin Cao, Guanghong Wei [Fudan University]

J. Phys. Chem. B., **118**, 6733–6741, 2014.

Alzheimer's disease (AD) is associated with the pathological self-assembly of amyloid- β (A β) peptides into β -sheet-rich oligomers and insoluble amyloid fibrils. Experimental studies reported that 1,2-(dimethoxymethano)fullerene (DMF), a water-soluble fullerene derivative, inhibits strongly A β peptide aggregation at the early stage. In this study, we have investigated the detailed interaction of a DMF molecule with a fibrillar hexamer of full-length A β 42 and the resulting structural alterations by performing multiple all-atom explicit solvent MD simulations.

Surface Adsorption and Bulk Aggregation of Cyclodextrins by Computational Molecular Dynamics Simulations as a Function of Temperature: α -CD vs β -CD

Edgar Mixcoha, José Campos-Terán, Ángel Piñeiro [Universidade de Santiago de Compostela]

J. Phys. Chem. B., **118**, 6999–7011, 2014.

The structural simplicity of native cyclodextrins (CDs) contrasts with their complex behavior in the bulk of aqueous solutions, mainly when they are combined with other cosolutes. Many scientific and industrial applications based on these molecules are supported only by empirical information. In order to fill these gaps, a detailed computational study on the adsorption and aggregation of α - and β -CDs as a function of temperature is presented here. Our simulations reproduce, at atomic resolution, the experimentally observed much higher ability of β -CD to aggregate compared to that of α -CD at 298 K, as well as their dependence on temperature.

Structural and Energetic Insight into the Cross-Seeding Amyloid Assemblies of Human IAPP and Rat IAPP

Mingzhen Zhang, Rundong Hu, Guizhao Liang, Yung Chang, Yan Sun, Zhenmeng Peng, Jie Zheng [The University of Akron]

J. Phys. Chem. B., **118**, 7026–7036, 2014.

The misfolding and aggregation of human islet amyloid polypeptide (hIAPP or amylin) into small oligomers and large amyloid fibrils is believed to be responsible for the dysfunction and death of pancreatic β -cells in diabetes type II. However, rat IAPP (rIAPP), which differs from the hIAPP by only 6 of 37 residues, lacks the ability to form amyloid fibrils and to induce cell death. Little is known about the cross-sequence interactions and cross-seeding structures between hIAPP and rIAPP peptides. Herein using explicit-solvent MD simulations, we modeled and simulated different heteroassemblies formed by the amyloidogenic hIAPP and the nonamyloidogenic rIAPP peptides.

Protein Dynamics (Cont'd)

Influence of Charged Groups on the Properties of Zwitterionic Moieties: A Molecular Simulation Study

Qing Shao , Shaoyi Jiang [University of Washington]

J. Phys. Chem. B., **118**, 7630–7637, 2014.

Zwitterionic carboxybetaine and sulfobetaine materials have shown an excellent ability to resist nonspecific protein adsorption. It is desirable to obtain a better understanding of zwitterionic materials based on their molecular structures. This work aims to understand the roles of charged groups in zwitterionic moieties and to design new protein-resistant zwitterionic moieties beyond carboxybetaine and sulfobetaine. We conducted molecular simulations to study the hydration, self-association, and protein interactions of 12 zwitterionic moieties derived from three anionic groups (carboxylic, sulfonate, and sulfate) and four cationic groups (quaternary ammonium, tertiary ammonium, secondary ammonium, and primary ammonium).

Computational Study of the Stability of the Miniprotein Trp-Cage, the GB1 β -Hairpin, and the AK16 Peptide, under Negative Pressure

Harold W. Hatch, Frank H. Stillinger, Pablo G. Debenedetti [Princeton University]

J. Phys. Chem. B., **118**, 7761–7769, 2014.

Although hot, cold, and high pressure denaturation are well characterized, the possibility of negative pressure unfolding has received much less attention. Proteins under negative pressure, however, are important in applications such as medical ultrasound, and the survival of biopolymers in the xylem and adjacent parenchyma cells of vascular plants. In addition, negative pressure unfolding is fundamentally important in obtaining a complete understanding of protein stability and naturally complements previous studies of high pressure denaturation.

Anisotropic Responses and Initial Decomposition of Condensed-Phase β -HMX under Shock Loadings via Molecular Dynamics Simulations in Conjunction with Multiscale Shock Technique

Ni-Na Ge, Yong-Kai Wei, Zhen-Fei Song, Xiang-Rong Chen, Guang-Fu Ji, Feng Zhao, Dong-Qing Wei [Beijing Institute of Technology]

J. Phys. Chem. B., **118**, 8691–8699, 2014.

Molecular dynamics simulations in conjunction with multiscale shock technique (MSST) are performed to study the initial chemical processes and the anisotropy of shock sensitivity of the condensed-phase HMX under shock loadings applied along the a, b, and c lattice vectors. A self-consistent charge density-functional tight-binding (SCC-DFTB) method was employed. Our results show that there is a difference between lattice vector a (or c) and lattice vector bin the response to a shock wave velocity of 11 km/s, which is investigated through reaction temperature and relative sliding rate between adjacent slipping planes.

Assembly of Amyloid β Peptides in the Presence of Fibril Seeds: One-Pot Coarse-Grained Molecular Dynamics Simulations

Liang Xu [Dalian University of Technology], Yonggang Chen, Xiaojuan Wang

J. Phys. Chem. B., **118**, 9238–9246, 2014.

The identification of a secondary nucleation pathway in the early aggregation of amyloid peptides suggests that the generation of toxic oligomers involves both monomers and preformed fibril seeds. To elucidate the underlying molecular mechanism, a set of one-pot coarse-grained molecular dynamics simulations was performed to investigate the self-assembly of amyloid β peptides in the presence of fibril seeds. It was observed that fibril seeds alone randomly assemble into an elongated protofibril, whereas monomers alone form an elongated globular oligomer with various morphologies.

Protein Dynamics (Cont'd)

An innovative synergistic grid approach to the computational study of protein aggregation mechanisms

Noelia Faginas-Lago [University of Perugia], Margarita Albertí, Alessandro Costantini, Antonio Laganà, Andrea Lombardi, Leonardo Pacifici

J. Mol.Mod., **20**, 2226, 2014.

Thanks to the advances in grid technologies, we are able to propose here an evolution of our molecular simulator that, when moving to larger systems, instead of reducing the granularity of the dynamical treatment (as is often done in molecular dynamics studies of such systems) exploits the extra power of the grid approach to the end of preserving the detailed nature of the atomistic formulation of the interaction. As a prototype case study, the *N*-methylacetamide dimer in vacuo has been considered and the formation of possible conformers is analyzed.

External electric field effects on the mechanical properties of the $\alpha\beta$ -tubulin dimer of microtubules: a molecular dynamics study

H. R. Saeidi, A. Lohrasebi [University of Isfahan], K. Mahnam

J. Mol.Mod., **20**, 2395, 2014.

The mechanical properties of the $\alpha\beta$ -tubulin dimer of microtubules was modeled by using the molecular dynamics (MD) simulation method. The effect on the mechanical properties of the dimer of the existence and nonexistence of an applied electric field, either constant or periodic, was studied. Since there are charged or polar groups in the dimer structure, the electric field can interact with the dimer. The elastic constant and Young's modulus of the dimer were decreased when the dimer was exposed to a constant electric field of 0.03 V/nm.

Role of pH in structural changes for Pin1 protein: an insight from molecular dynamics study

Yu Wang, Lei Xi, Jie Yao, Jiao Yang, Lin-Fang Du [Sichuan University]

J. Mol.Mod., **20**, 2376, 2014.

Pin1 protein is closely associated with the pathogenesis of cancers and Alzheimer's disease (AD). Previously, we have shown the acid-induced denaturation of Pin1 was determined by means of fluorescence emission, synchronous fluorescence etc., indicating an intermediate state around chromophores in Pin1 at about 4.0. Molecular dynamics simulations for the wild type Pin1 and its mutants were performed to explore the role of pH in the conformation changes of Pin1 protein.

Molecular dynamics studies on the influences of a gradient electric field on the water chain in a peptide nanotube

Hui Li, Jianfen F. Fan [Soochow University,], Rui Li, Yi Yu, Xiliang L. Yan

J. Mol.Mod., **20**, 2370, 2014.

The structure and transportation characteristics of the water chain inside a $8 \times \text{cyclo-(WL)}_4$ peptide nanotube (PNT) were simulated under a gradient electric (GE) field. The gradient was defined by the ratio of a constant (E_a) and the z-directional length (L_z) of the simulation box. E_a varies from 0.0 to 0.9 V nm⁻¹. As the gradient increases, the probabilities of finding two water molecules in an α -plane zone and three in a midplane region increase. To accommodate more water molecules, the axial array of channel water molecules becomes more compact.

Free Energy Calculation

Free Energy Predictions of Ligand Binding to an α -Helix Using Steered Molecular Dynamics and Umbrella Sampling Simulations

Jan K. Marzinek, Peter J. Bond, Guoping Lian, Yanyan Zhao, Lujia Han, Massimo G. Noro, Efstratios N. Pistikopoulos, Athanasios Mantalaris [Imperial College London]

J.Chem. Infor. and Mod. **54**, 2093–2104, 2014.

Free energy prediction of ligand binding to macromolecules using explicit solvent molecular dynamics (MD) simulations is computationally very expensive. In this work, the generality of the linear correlation is further tested for several ligands interacting with the α -helical motif of keratin. Using the constant loading rate of our previous study of the keratin-EGCG system, we observe that the linear correlation for keratin-EGCG can be extended to other uncharged molecules where interactions are governed by hydrogen bonds and/or a combination of hydrogen bonds and hydrophobic forces.

Improved Reweighting of Accelerated Molecular Dynamics Simulations for Free Energy Calculation

Yinglong Miao [University of California at San Diego], William Sinko, Levi Pierce, Denis Bucher, Ross C. Walker, J. Andrew McCammon

J. Chem. Theor. and Comp. **10**, 2677–2689, 2014.

Accelerated molecular dynamics (aMD) simulations greatly improve the efficiency of conventional molecular dynamics (cMD) for sampling biomolecular conformations, but they require proper reweighting for free energy calculation. In this work, we systematically compare the accuracy of different reweighting algorithms including the exponential average, Maclaurin series, and cumulant expansion on three model systems: alanine dipeptide, chignolin, and Trp-cage. Exponential average reweighting can recover the original free energy profiles easily only when the distribution of the boost potential is narrow (e.g., the range $\leq 20kBT$) as found in dihedral-boost aMD simulation of alanine dipeptide.

An Overview of Electrostatic Free Energy Computations for Solutions and Proteins

Yen-Lin Lin, Alexey Aleksandrov, Thomas Simonson, Benoît Roux [University of Chicago]

J. Chem. Theor. and Comp. **10**, 2690–2709, 2014.

Free energy simulations for electrostatic and charging processes in complex molecular systems encounter specific difficulties owing to the long-range, $1/r$ Coulomb interaction. To calculate the solvation free energy of a simple ion, it is essential to take into account the polarization of nearby solvent but also the electrostatic potential drop across the liquid–gas boundary, however distant. The latter does not exist in a simulation model based on periodic boundary conditions because there is no physical boundary to the system.

Integrated Hamiltonian Sampling: A Simple and Versatile Method for Free Energy Simulations and Conformational Sampling

Toshifumi Mori, Robert J. Hamers, Joel A. Pedersen, Qiang Cui [University Avenue, Madison]

J. Phys. Chem. B. **118**, 8210–8220, 2014.

Motivated by specific applications and the recent work of Gao and co-workers on integrated tempering sampling (ITS), we have developed a novel sampling approach referred to as integrated Hamiltonian sampling (IHS). IHS is straightforward to implement and complementary to existing methods for free energy simulation and enhanced configurational sampling. The method carries out sampling using an effective Hamiltonian constructed by integrating the Boltzmann distributions of a series of Hamiltonians.

Ligand Binding/Docking

molBLOCKS: decomposing small molecule sets and uncovering enriched fragments

Dario Gherzi, Mona Singh [Princeton University]

Bioinformatics, **30**, 2081–2083, 2014.

The chemical structures of biomolecules, whether naturally occurring or synthetic, are composed of functionally important building blocks. Given a set of small molecules—for example, those known to bind a particular protein—computationally decomposing them into chemically meaningful fragments can help elucidate their functional properties, and may be useful for designing novel compounds with similar properties. Here we introduce molBLOCKS, a suite of programs for breaking down sets of small molecules into fragments according to a predefined set of chemical rules, clustering the resulting fragments, and uncovering statistically enriched fragments.

Position of Transmembrane Helix 6 Determines Receptor G Protein Coupling Specificity

Alexander S. Rose, Matthias Elgeti, Ulrich Zachariae, Helmut Grubmüller, Klaus Peter Hofmann, Patrick Scheerer, Peter W. Hildebrand [Charité—Universitätsmedizin Berlin]

J. Am. Chem. Soc., 2013, **136**, 11244–11247, 2014.

G protein coupled receptors (GPCRs) transmit extracellular signals into the cell by binding and activating different intracellular signaling proteins, such as G proteins ($G\alpha\beta\gamma$, families G_i , G_s , G_q , $G_{12/13}$) or arrestins. To address the issue of G_s vs G_i coupling specificity, we carried out molecular dynamics simulations of lipid-embedded active β_2 -adrenoceptor (β_2AR^*) in complex with C-terminal peptides derived from the key interaction site of $G\alpha$ ($G\alpha CT$) as surrogate of $G\alpha\beta\gamma$. We find that $G_i\alpha CT$ and $G_s\alpha CT$ exploit distinct cytoplasmic receptor conformations that coexist in the uncomplexed β_2AR^* .

A Molecular modeling study of the changes of some steric properties of the precatalysts during the olefin metathesis reaction

Frans T. I. Marx, Johan H. L. Jordaan [North-West University], Gerhard Lachmann, Hermanus C. M. Vosloo

J. Comp. Chem., **35**, 1457–1463, 2014.

The productive self-metathesis of 1-octene with a series of new phosphine ligated Grubbs-type precatalysts was studied. The resulting structures were used to compare some steric properties of the new precatalysts with those of well-known precatalysts. The possibility of α -CC agnostic stabilization as well as the ability of the ligands to shield the metal was studied. A comparison of the obtained data, pointed to the unlikelihood that α -CC agostic stabilization is a major contribution to the stabilization of the various metallacyclobutane rings.

Radioiodinated Benzyloxybenzene Derivatives: A Class of Flexible Ligands Target to β -Amyloid Plaques in Alzheimer's Brains

Yanping Yang, Mengchao Cui [Beijing Normal University], Xiaoyang Zhang, Jiawei Dai, Zhiyong Zhang, Chunping Lin, Yuzhi Guo, Boli Liu

J. Med. Chem., **57**, 6030–6042, 2014.

Benzyloxybenzene, as a novel flexible scaffold without rigid planarity, was synthesized and evaluated as ligand toward $A\beta$ plaques. The binding site calculated for these flexible ligands was the hydrophobic Val18_Phe20 channel on the flat surface of $A\beta$ fiber. Structure–activity relationship analysis generated a common trend that binding affinities declined significantly from para-substituted ligands to ortho-substituted ones, which was also quantitatively illustrated by 3D-QSAR modeling.

Ligand Binding / Docking (Cont'd)

Best of Both Worlds: On the Complementarity of Ligand-Based and Structure-Based Virtual Screening

Fabio Broccatelli , Nathan Brown [The Institute of Cancer Research, London]

J.Chem. Infor. and Mod. **54**, 1634–1641, 2014.

Virtual screening with docking is an integral component of drug design, particularly during hit finding phases. While successful prospective studies of virtual screening exist, it remains a significant challenge to identify best practices a priori due to the many factors that influence the final outcome, including targets, data sets, software, metrics, and expert knowledge of the users. We investigate the extent to which ligand-based methods can be applied to improve structure-based methods. The use of ligand-based methods to modulate the number of hits identified using the protein–ligand complex from the crystallographic ligand is discussed.

Prediction of Substrates for Glutathione Transferases by Covalent Docking

Guang Qiang Dong, Sara Calhoun, Hao Fan, Chakrapani Kalyanaraman, Megan C. Branch, Susan T. Mashiyama, Nir London, Matthew P. Jacobson, Patricia C. Babbitt, Brian K. Shoichet, Richard N. Armstrong, Andrej Sali [University of California at San Francisco]

J.Chem. Infor. and Mod. **54**, 1687–1699, 2014.

Enzymes in the glutathione transferase (GST) superfamily catalyze the conjugation of glutathione (GSH) to electrophilic substrates. As a consequence they are involved in a number of key biological processes, including protection of cells against chemical damage, steroid and prostaglandin biosynthesis, tyrosine catabolism, and cell apoptosis. In this study, we investigate the accuracy of docking poses and substrate discovery in the GST superfamily, by docking 6738 potential ligands from the KEGG and MetaCyc compound libraries into 14 representative GST enzymes with known substrates using the PLOP program.

Structure-Based Virtual Screening Approach for Discovery of Covalently Bound Ligands

Dora Toledo Warshaviak, Gali Golan, Kenneth W. Borrelli, Kai Zhu, Ori Kalid [Karyopharm Therapeutics]

J.Chem. Infor. and Mod. **54**, 1941–1950, 2014.

We were able to retrieve 71%, 72%, and 77% of the known actives for Cathepsin K, HCV NS3 protease, and EGFR within 5% of the decoy library, respectively. With the more challenging XPO1 target, where no specific interactions with the protein could be used for postprocessing of the docking results, we were able to retrieve 95% of the actives within 30% of the decoy library and achieved an early enrichment factor (EF1%) of 33. The poses of the known actives bound to existing crystal structures of 4 targets were predicted with an average RMSD of 1.9 Å. To the best of our knowledge, CovDock-VS is the first fully automated tool for efficient virtual screening of covalent inhibitors.

Strategies for Improved Modeling of GPCR-Drug Complexes: Blind Predictions of Serotonin Receptors Bound to Ergotamine

David Rodríguez, Anirudh Ranganathan, Jens Carlsson [Stockholm University]

J.Chem. Infor. and Mod. **54**, 2004–2021, 2014.

The recent increase in the number of atomic-resolution structures of G protein-coupled receptors (GPCRs) has lead to a deeper understanding of ligand binding to drug targets. However, reliable modeling of GPCR-ligand complexes for the vast majority of receptors with unknown structure remains to be one of the most challenging goals for computer-aided drug design. The GPCR Dock 2013 assessment, in which researchers were challenged to predict the crystallographic structures of serotonin 5-HT1B and 5-HT2B receptors bound to ergotamine, provided an excellent opportunity to benchmark the current state of this field.

Ligand Binding / Docking (Cont'd)

Docking Server for the Identification of Heparin Binding Sites on Proteins

Scott E. Mottarella, Dmitri Beglov, Natalia Beglova, Matthew A. Nugent, Dima Kozakov, Sandor Vajda [Boston University]

J.Chem. Infor. and Mod. **54**, 2068–2078, 2014.

Many proteins of widely differing functionality and structure are capable of binding heparin and heparan sulfate. Since crystallizing protein–heparin complexes for structure determination is generally difficult, computational docking can be a useful approach for understanding specific interactions. Previous studies used programs originally developed for docking small molecules to well-defined pockets, rather than for docking polysaccharides to highly charged shallow crevices that usually bind heparin. We have extended the program PIPER and the automated protein–protein docking server ClusPro to heparin docking.

Relative Binding Enthalpies from Molecular Dynamics Simulations Using a Direct Method

Amitava Roy, Duy P. Hua, Joshua M. Ward, Carol Beth Post [Purdue University]

J. Chem. Theor. and Comp. **10**, 2759–2768, 2014.

The potential for reliably predicting relative binding enthalpies, $\Delta\Delta E$, from a direct method utilizing molecular dynamics is examined for a system of three phosphotyrosyl peptides binding to a protein receptor, the Src SH2 domain. The binding enthalpies were calculated from the potential energy differences between the bound and the unbound end-states of each peptide from equilibrium simulations in explicit water. The statistical uncertainties in the ensemble-mean energy values from multiple, independent simulations were obtained using a bootstrap method. Simulations were initiated with different starting coordinates as well as different velocities.

Free Energy Calculations for the Peripheral Binding of Proteins/Peptides to an Anionic Membrane. 1. Implicit Membrane Models

Leili Zhang, Arun Yethiraj, Qiang Cui [University of Wisconsin-Madison]

J. Chem. Theor. and Comp. **10**, 2845–2859, 2014.

The binding of peptides and proteins to the surface of complex lipid membranes is important in many biological processes such as cell signaling and membrane remodeling. Computational studies can aid experiments by identifying physical interactions and structural motifs that determine the binding affinity and specificity. We show that the binding free energy can be efficiently computed following a thermodynamic cycle similar to protein–ligand binding calculations, especially when a Bennett acceptance ratio based protocol is used to consider both the membrane bound and solution conformational ensembles.

Interaction of Extracellular Loop II of κ -Opioid Receptor (196–228) with Opioid Peptide Dynorphin in Membrane Environments as Revealed by Solid State Nuclear Magnetic Resonance, Quartz Crystal Microbalance and Molecular Dynamics Simulation

Atsushi Kira, Namsrai Javkhlantugs, Takenori Miyamori, Yoshiyuki Sasaki, Masayuki Eguchi, Izuru Kawamura, Kazuyoshi Ueda, Akira Naito [Yokohama National University]

J. Phys. Chem. B. **118**, 9604–9612, 2014.

Extracellular loop II (ECL-II) of the κ -opioid receptor displays an amphiphilic helix in membrane environments and the N-terminal α -helix of dynorphin A(1–17) (hereafter DynA17) is inserted into the membrane with the tilt angle of 21° to the bilayer normal. ECL-II peptides (1–33), corresponding to 196–228 of κ -opioid receptor with [1-¹³C]- or [3-¹³C]-labeled amino acids were incorporated into large [dimyristoylphosphatidyl choline (DMPC)/ dihexanoylphosphatidyl choline (DHPC) = 3, q = 3] and small bicelle (q = 1) systems.

Ligand Binding / Docking (Cont'd)

Structural and functional alterations of myoglobin by glucose-protein interactions

Yong You, Fang Liu, Ke-Jie Du, Ge-Bo Wen [University of South China], Ying-Wu Lin

J. Mol.Mod., **20**, 2358, 2014.

The interaction of blood glucose with heme proteins plays a key role in inducing diabetes, a serious disease threatening human health. In this study, we investigated the non-covalent interaction between glucose and myoglobin (Mb), both theoretically and experimentally, using molecular dynamics (MD) simulation combined with spectroscopic studies. It revealed that glucoses can occupy the side pocket of Mb, and bind closely to one of the xenon cavities in Mb, by hydrogen bonding interactions with two propionate groups of heme as well as surrounding amino acids.

Effects of the protonation state in the interaction of an HIV-1 reverse transcriptase (RT) amino acid, Lys101, and a non nucleoside RT inhibitor, GW420867X

Sérgio E. Galembeck [Departamento de Química], F. Matthias Bickelhaupt, Célia Fonseca Guerra, Eduardo Galembeck

J. Mol.Mod., **20**, 2332, 2014.

Interactions between an inhibitor and amino acids from a binding pocket could help not only to understand the nature of these interactions, but also to support the design of new inhibitors. In this paper, we explore the key interaction between a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI), GW420867X, and HIV-1 RT amino acid Lys101 (K101), by quantum mechanical methods. The neutral, protonated, and zwitterionic complexes of GW420867X–K101 were studied.

Binding-competent states for L-arginine in *E. coli* arginine repressor apoprotein

Saurabh Kumar Pandey, David Řeha, Vasilina Zayats, Milan Melicherčík, Jannette Carey, Rüdiger Ettrich [Academy of Sciences of the Czech Republic]

J. Mol.Mod., **20**, 2330, 2014.

Arginine repressor of *E. coli* is a multifunctional hexameric protein that provides feedback regulation of arginine metabolism upon activation by the negatively cooperative binding of L-arginine. Interpretation of this complex system requires an understanding of the protein's conformational landscape. The ~50 kDa hexameric C-terminal domain was studied by 100 ns molecular dynamics simulations in the presence and absence of the six L-arg ligands that bind at the trimer-trimer interface.

Understanding electrostatic and steric requirements related to hypertensive action of AT₁ antagonists using molecular modeling techniques

Danielle da C. Silva, Vinicius G. Maltarollo, Emmanuela Ferreira de Lima, Karen Cacilda Weber, Kathia M. Honório [Universidade Federal do ABC]

J. Mol.Mod., **20**, 2231, 2014.

AT₁ receptor is an interesting biological target involved in several important diseases, such as blood hypertension and cardiovascular pathologies. In this study we investigated the main electrostatic and steric features of a series of AT₁ antagonists related to hypertensive activity using structure and ligand-based strategies (docking and CoMFA). The generated 3D model had good internal and external consistency and was used to predict the potency of an external test set. The predicted values of pIC₅₀ are in good agreement with the experimental results of biological activity, indicating that the 3D model can be used to predict the biological property of untested compounds.

Ligand Binding / Docking (Cont'd)

A study of the interaction between HIV-1 protease and C_2 -symmetric inhibitors by computational methods

Shuhua Shi, Guodong Hu [Dezhou University], Xiumei Zhang, Jihua Wang

J. Mol.Mod., **20**, 2369, 2014.

The human immunodeficiency virus type 1 protease (HIV-1 PR) is a major target for the design of anti-AIDS (acquired immune deficiency syndrome) drugs. Some C_2 -symmetric inhibitors have been designed for the C_2 -symmetric binding pocket of HIV-1PR. The crystallographic structures reveal that the binding modes are not C_2 -symmetric for C_2 -symmetric inhibitors binding to PR. In this work, four molecular dynamics (MD) simulations were performed to investigate the binding modes between four C_2 -symmetric inhibitors (6 AD, 6AG, 6FD and 6FG) and PR, as well as the stabilities of these inhibitors in the binding pocket.

Protein tyrosine phosphatases: Ligand interaction analysis and optimisation of virtual screening

Mohammad A. Ghattas, Noor Atatreh, Elena V. Bichenkova, Richard A. Bryce [University of Mancheste]

J. Mol.Graph. and Mod., **52**, 114-123, 2014.

Docking-based virtual screening is an established component of structure-based drug discovery. Nevertheless, scoring and ranking of computationally docked ligand libraries still suffer from many false positives. Identifying optimal docking parameters for a target protein prior to virtual screening can improve experimental hit rates. Here, we examine protocols for virtual screening against the important but challenging class of drug target, protein tyrosine phosphatases. In this study, common interaction features were identified from analysis of protein–ligand binding geometries of more than 50 complexed phosphatase crystal structures.

Enzyme Catalysis

Carbohydrate–Protein Interactions That Drive Processive Polysaccharide Translocation in Enzymes Revealed from a Computational Study of Cellobiohydrolase Processivity

Brandon C. Knott, Michael F. Crowley, Michael E. Himmel, Jerry Ståhlberg, Gregg T. Beckham [National Renewable Energy Laboratory, Golden]

J. Am. Chem. Soc., 2013, **136**, 8810–8819, 2014.

Translocation of carbohydrate polymers through protein tunnels and clefts is a ubiquitous biochemical phenomenon in proteins such as polysaccharide synthases, glycoside hydrolases, and carbohydrate-binding modules. Our results demonstrate that these biologically and industrially important enzymes employ a two-step mechanism for chain threading to form a Michaelis complex and that the free energy barrier to chain threading is significantly lower than the hydrolysis barrier. Based on the simulations, we find that strong electrostatic interactions with polar residues that are conserved in GH7 cellobiohydrolases, but not in GH7 endoglucanases, at the leading glucosyl ring provide the thermodynamic driving force for polysaccharide chain translocation.

Enzyme Catalysis (Cont'd)

Substrate-mediated proton relay mechanism for the religation reaction in topoisomerase II

Kyohei Hanaoka [University of Tsukuba], Mitsuo Shoji, Daiki Kondo, Akimasa Sato, Moon Young Yang, Katsumasa Kamiya, Kenji Shiraishi

J. Biomol. Stru. and Dyn., 32, 1759-1765, 2014.

The DNA religation reaction of yeast type II topoisomerase (topo II) was investigated to elucidate its metal-dependent general acid/base catalysis. Quantum mechanical/molecular mechanical calculations were performed for the topo II religation reaction, and the proton transfer pathway was examined. We found a substrate-mediated proton transfer of the topo II religation reaction, which involves the 3' OH nucleophile, the reactive phosphate, water, Arg781, and Tyr782. Metal A stabilizes the transition states, which is consistent with a two-metal mechanism in topo II.

Structural insight into exosite binding and discovery of novel exosite inhibitors of botulinum neurotoxin serotype A through in silico screening

Xin Hu [National Institutes of Health, Rockville] Patricia M. Legler, Noel Southall, David J. Maloney, Anton Simeonov, Ajit Jadhav

J. Comp. Aided. Mol. Design, 28, 765-778, 2014.

Botulinum neurotoxin serotype A (BoNT/A) is the most lethal toxin among the Tier 1 Select Agents. In this study, we employed two recently identified exosite inhibitors, D-chicoric acid and lomofungin, to probe the structural features of the exosites and molecular mechanisms of synergistic inhibition. The results showed that D-chicoric acid favors binding at the α -exosite, whereas lomofungin preferentially binds at the β -exosite by mimicking the substrate β -sheet binding interaction. Molecular dynamics simulations and binding interaction analysis of the exosite inhibitors with BoNT/A revealed key elements and hotspots that likely contribute to the inhibitor binding and synergistic inhibition.

Design of a colicin E7 based chimeric zinc-finger nuclease

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J. Comp. Aided. Mol. Design, 28, 841-850, 2014.

Colicin E7 is a natural bacterial toxin. Its nuclease domain (NColE7) enters the target cell and kills it by digesting the nucleic acids. The HNH-motif as the catalytic centre of NColE7 at the C-terminus requires the positively charged N-terminal loop for the nuclease activity—offering opportunities for allosteric control in a NColE7-based artificial nuclease. Accordingly, four novel zinc finger nucleases were designed by computational methods exploiting the special structural features of NColE7. The constructed models were subjected to MD simulations.

Lid Closure Mechanism of Yarrowia lipolytica Lipase in Methanol Investigated by Molecular Dynamics Simulation

Yang Jiang, Lingli Li, Haiyang Zhang, Wei Feng, Tianwei Tan [Beijing University of Chemical Technology]

J. Chem. Infor. and Mod. 54, 2033–2041, 2014.

In nonaqueous organic solvents, lipases can catalyze esterification reactions, which increase their application value. *Yarrowia lipolytica* Lipase (Lip2) possesses potential values in medicine and industrial production. In order to investigate its lid closure mechanism in methanol we performed molecular dynamics (MD) simulations of the open conformation of Lip2 in methanol and hexane, respectively. Simulation results indicated that Lip2 undergoes a greater conformational change in methanol. Principle component analysis showed Lip2 has “double-domain” and “torsion” motion modes in hexane and methanol.

Enzyme Catalysis (Cont'd)

Computationally Efficient and Accurate Enantioselectivity Modeling by Clusters of Molecular Dynamics Simulations

Hein J. Wijma, Siewert J. Marrink, Dick B. Janssen
[University of Groningen]

J.Chem. Infor. and Mod. **54**, 2079–2092, 2014.

Computational approaches could decrease the need for the laborious high-throughput experimental screening that is often required to improve enzymes by mutagenesis. Here, we report that using multiple short molecular dynamics (MD) simulations makes it possible to accurately model enantioselectivity for large numbers of enzyme–substrate combinations at low computational costs. We chose four different haloalkane dehalogenases as model systems because of the availability of a large set of experimental data on the enantioselective conversion of 45 different substrates.

Evaluation of active designs of cephalosporin C acylase by molecular dynamics simulation and molecular docking

Qing Li, Xiaoqiang Huang, Yushan Zhu [Tsinghua University]

J. Mol.Mod., **20**, 2314, 2014.

Optimization to identify the global minimum energy conformation sequence in in silico enzyme design is computationally non-deterministic polynomial-time (NP)-hard, with the search time growing exponentially as the number of design sites increases. In this report, cephalosporin acylase, which catalyzes the hydrolytic reaction of cephalosporin C to 7-aminocephalosporanic acid, was used to investigate the dynamic features of active-site-transition-state complex structures using molecular dynamics (MD) simulations to potentially eliminate false positives.

Protein-Protein Interactions

Exploration of protein–protein interaction effects on α -2-macroglobulin in an inhibition of serine protease through gene expression and molecular simulations studies

Jeyachandran Sivakamavalli, Chandrabose Selvaraj, Sanjeev Kumar Singh, Baskaralingam Vaseeharan [Alagappa University]

J. Biomol. Stru. and Dyn., **32**, 1841-1854, 2014.

In Prophenoloxidase (ProPO) cascade, two targets namely serine protease and α -2-macroglobulin are key regulators involved in the defense system of crustaceans. In biological systems, routine role of cell systems requires the understanding in protein–protein interactions through experimental and theoretical concepts, which might yield useful insights into the cellular responses. Response of cells to regulating the immune system is governed by the interactions-involved biomolecular simulations. Unfortunately, studies on the inhibitors (SP and α -2M) that negatively regulate the proPO system or melanization in penaeid shrimp are not yet available.

Membrane Proteins and Lipid Peptide Interactions

ProQM-resample: improved model quality assessment for membrane proteins by limited conformational sampling

Björn Wallner [Linköping University]

Bioinformatics. **30**, 2221-2223, 2014.

Model Quality Assessment Programs (MQAPs) are used to predict the quality of modeled protein structures. These usually use two approaches: methods using consensus of many alternative models and methods requiring only a single model to do its prediction. The consensus methods are useful to improve overall accuracy; however, they frequently fail to pick out the best possible model and cannot be used to generate and score new structures. . Here, we present *ProQM-resample*, a membrane protein-specific single-model MQAP, that couples side-chain resampling with MQAP rescoring by ProQM to improve model selection.

CHARMM All-Atom Additive Force Field for Sphingomyelin: Elucidation of Hydrogen Bonding and of Positive Curvature

Richard M. Venable, Alexander J. Sodt, Brent Rogaski, Huan Rui, Elizabeth Hatcher, Alexander D. MacKerell Jr., Richard W. Pastor, Jeffery B. Klauda [University of Maryland]

Biophysical Journal. **107**, 134-145, 2014.

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The present simulations reveal O-H:::O-P intralipid hydrogen bonding occurs 99% of the time, and interlipid N-H:::O=C (26-29%, depending on the lipid) and N-H:::O-H (17-19%). The interlipid hydrogen bonds are long lived, showing decay times of 50 ns, and forming strings of lipids, and leading to reorientational correlation time of nearly 100 ns. The spontaneous radius of curvature for pure *N*-palmitoyl sphingomyelin bilayers is estimated to be 43-100 Å, depending on the assumptions made in assigning a bending constant; this unusual positive curvature for a two-tailed neutral lipid is likely associated with hydrogen bond networks involving the NH of the sphingosine group.

A Method to Predict Blood-Brain Barrier Permeability of Drug-Like Compounds Using Molecular Dynamics Simulations

Timothy S. Carpenter, Daniel A. Kirshner, Edmond Y. Lau, Sergio E. Wong, Jerome P. Nilmeier, Felice C. Lightstone [Lawrence Livermore National Laboratory]

Biophysical Journal. **107**, 630-641, 2014.

The blood-brain barrier (BBB) is formed by specialized tight junctions between endothelial cells that line brain capillaries to create a highly selective barrier between the brain and the rest of the body. A major problem to overcome in drug design is the ability of the compound in question to cross the BBB. Neuroactive drugs are required to cross the BBB to function. Conversely, drugs that target other parts of the body ideally should not cross the BBB to avoid possible psychotropic side effects. Thus, the task of predicting the BBB permeability of new compounds is of great importance.

Structure of the Neisserial Outer Membrane Protein Opa60: Loop Flexibility Essential to Receptor Recognition and Bacterial Engulfment

Daniel A. Fox, Per Larsson, Ryan H. Lo, Brett M. Kroncke, Peter M. Kasson, Linda Columbus [University of Virginia]

J. Am. Chem. Soc., 2013, **136**, 9938-9946, 2014.

The structure and dynamics of Opa proteins, which we report herein, are responsible for the receptor-mediated engulfment of *Neisseria gonorrhoeae* or *Neisseria meningitidis* by human cells and can offer deep understanding into the molecular recognition of pathogen-host receptor interactions. Such interactions are vital to understanding bacterial pathogenesis as well as the mechanism of foreign body entry to a human cell, which may provide insights for the development of targeted pharmaceutical delivery systems.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Indentation and Self-Healing Mechanisms of a Self-Assembled Monolayer—A Combined Experimental and Modeling Study

Christian Meltzer, Jonas Paul, Hanno Dietrich, Christof M. Jäger, Timothy Clark, Dirk Zahn, Björn Braunschweig, Wolfgang Peukert [Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU)]

J. Am. Chem. Soc., 2013, **136**, 10718–10727, 2014.

A combination of in situ vibrational sum-frequency generation (SFG) spectroscopy and molecular-dynamics (MD) simulations has allowed us to study the effects of indentation of self-assembled octadecylphosphonic acid (ODPA) monolayers on α -Al₂O₃(0001). Stress-induced changes in the vibrational signatures of C–H stretching vibrations in SFG spectra and the results of MD simulations provide clear evidence for an increase in gauche-defect density in the monolayer as a response to indentation. A stress-dependent analysis indicates that the defect density reaches saturation at approximately 155 MPa. After stress is released, the MD simulations show an almost instantaneous healing of pressure-induced defects in good agreement with experimental results.

Membrane undulation induced by NS4A of Dengue virus: a molecular dynamics simulation study

Meng-Han Lin, Hao-Jen Hsu, Ralf Bartenschlager, Wolfgang B. Fischer [National Yang-Ming University]

J. Biomol. Stru. and Dyn., 32, 1552-1562, 2014.

Nonstructural protein 4A (NS4A) of Dengue virus (DENV) is a membrane protein involved in rearrangements of the endoplasmic reticulum membrane that are required for formation of replication vesicles. NS4A is composed most likely of three membrane domains. The N- and C-terminal domains are supposed to traverse the lipid membrane whereas the central one is thought to reside on the membrane surface, thus forming a *u*-shaped protein. All three membrane domains are proposed to be helical by secondary structure prediction programs.

Strategies to Calculate Water Binding Free Energies in Protein–Ligand Complexes

Michael S. Bodnarchuk, Russell Viner, Julien Michel, Jonathan W. Essex [University of Southampton]

J. Chem. Infor. and Mod. **54**, 1623–1633, 2014.

Water molecules are commonplace in protein binding pockets, where they can typically form a complex between the protein and a ligand or become displaced upon ligand binding. As a result, it is often of great interest to establish both the binding free energy and location of such molecules. We report here a comparison between three such methodologies, Just Add Water Molecules (JAWS), Grand Canonical Monte Carlo (GCMC), and double-decoupling, in the hope of understanding the advantages and limitations of each method when applied to enclosed binding sites.

Protein–Ligand Docking Using Hamiltonian Replica Exchange Simulations with Soft Core Potentials

Manuel P. Luitz, Martin Zacharias [Technische Universität München]

J. Chem. Infor. and Mod. **54**, 1669–1675, 2014.

Molecular dynamics (MD) simulations in explicit solvent allow studying receptor–ligand binding processes including full flexibility of the binding partners and an explicit inclusion of solvation effects. However, in MD simulations, the search for an optimal ligand–receptor complex geometry is frequently trapped in locally stable non-native binding geometries. A Hamiltonian replica-exchange (H-REMD)-based protocol has been designed to enhance the sampling of putative ligand–receptor complexes.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Comparative Assessment of Scoring Functions on an Updated Benchmark: 2. Evaluation Methods and General Results

Yan Li, Li Han, Zhihai Liu, Renxiao Wang [Chinese Academy of Sciences]

J.Chem. Infor. and Mod. **54**, 1717–1736, 2014.

Our comparative assessment of scoring functions (CASF) benchmark is created to provide an objective evaluation of current scoring functions. The key idea of CASF is to compare the general performance of scoring functions on a diverse set of protein–ligand complexes. In order to avoid testing scoring functions in the context of molecular docking, the scoring process is separated from the docking (or sampling) process by using ensembles of ligand binding poses that are generated in prior. Here, we describe the technical methods and evaluation results of the latest CASF-2013 study.

sc-PDB-Frag: A Database of Protein–Ligand Interaction Patterns for Bioisosteric Replacements

Jérémy Desaphy , Didier Rognan [UMR 7200 Université de Strasbourg/CNRS]

J.Chem. Infor. and Mod. **54**, 1908–1918, 2014.

Bioisosteric replacement plays an important role in medicinal chemistry by keeping the biological activity of a molecule while changing either its core scaffold or substituents, thereby facilitating lead optimization and patenting. Bioisosteres are classically chosen in order to keep the main pharmacophoric moieties of the substructure to replace. However, notably when changing a scaffold, no attention is usually paid as whether all atoms of the reference scaffold are equally important for binding to the desired target.

Docking Covalent Inhibitors: A Parameter Free Approach To Pose Prediction and Scoring

Kai Zhu, Kenneth W. Borrelli, Jeremy R. Greenwood, Tyler Day, Robert Abel, Ramy S. Farid, Edward Harder [Schrodinger Inc]

J.Chem. Infor. and Mod. **54**, 1932–1940, 2014.

Although many popular docking programs include a facility to account for covalent ligands, large-scale systematic docking validation studies of covalent inhibitors have been sparse. In this paper, we present the development and validation of a novel approach for docking and scoring covalent inhibitors, which consists of conventional noncovalent docking, heuristic formation of the covalent attachment point, and structural refinement of the protein–ligand complex. This approach combines the strengths of the docking program Glide and the protein structure modeling program Prime and does not require any parameter fitting for the study of additional covalent reaction types.

Indirect Readout in Protein-Peptide Recognition: A Different Story from Classical Biomolecular Recognition

Hua Yu, Peng Zhou, Maolin Deng, Zhicai Shang [Zhejiang University]

J.Chem. Infor. and Mod. **54**, 2022–2032, 2014.

Protein-peptide interactions are prevalent and play essential roles in many living activities. Peptides recognize their protein partners by direct nonbonded interactions and indirect adjustment of conformations. Although processes of protein-peptide recognition have been comprehensively studied in both sequences and structures recently, flexibility of peptides and the configuration entropy penalty in recognition did not get enough attention. In this study, 20 protein-peptide complexes and their corresponding unbound peptides were investigated by molecular dynamics simulations.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Ensemble-Based Docking Using Biased Molecular Dynamics

Arthur J. Campbell, Michelle L. Lamb, Diane Joseph-McCarthy [AstraZeneca, R&D Boston]

J.Chem. Infor. and Mod. **54**, 2127–2138, 2014.

Proteins are dynamic molecules, and understanding their movements, especially as they relate to molecular recognition and protein–ligand interactions, poses a significant challenge to structure-based drug discovery. In most instances, protein flexibility is underrepresented in computer-aided drug design due to uncertainties on how it should be accurately modeled as well as the computational cost associated with attempting to incorporate flexibility in the calculations. Here we present a novel approach that uses biased-MD simulations to generate the docking ensemble.

Consensus Scoring Approach To Identify the Inhibitors of AMP-Activated Protein Kinase $\alpha 2$ with Virtual Screening

Hwangseo Park, Jae-Won Eom, Yang-Hee Kim [Sejong University]

J.Chem. Infor. and Mod. **54**, 2139–2146, 2014.

Due to the involvement in the ischemic damage in the brain, 5'-adenosine monophosphate-activated protein kinase subunit $\alpha 2$ (AMPK2) serves as a promising target for the development of new medicines for stroke. We aim in this study to identify a new class of AMPK2 inhibitors based on the structure-based virtual screening with docking simulations. To take advantage of and supplement the deficiencies of force field-based and empirical scoring functions, a consensus scoring method is employed to select the putative inhibitors by the combined use of AutoDock and FlexX programs.

Diffusive Models of Membrane Permeation with Explicit Orientational Freedom

Jeffrey Comer, Klaus Schulten, Christophe Chipot [Université de Lorraine]

J. Chem. Theor. and Comp. **10**, 2710–2718, 2014.

Accurate calculation of permeabilities from first-principles has been a long-standing challenge for computer simulations, notably in the context of drug discovery, as a route to predict the propensity of small, organic molecules to spontaneously translocate biological membranes. Of equal importance is the understanding of the permeation process and the pathway followed by the permeant from the aqueous medium to the interior of the lipid bilayer, and back out again. Here, we develop a formalism that includes an explicit description of the orientational motion of the solute as it diffuses across the membrane.

The Effects of Flanking Sequences in the Interaction of Polyglutamine Peptides with a Membrane Bilayer

Anu Nagarajan, Sudi Jawahery, Silvina Matysiak [University of Maryland]

J. Phys. Chem. B. **118**, 6368–6379, 2014.

Huntington's disease (HD) is caused by the presence of an extended polyglutamine (polyQ) region at the N-terminus of the huntingtin (htt) protein. The presence of flanking sequences adjacent to the polyQ region has been reported to modulate the effects of potentially toxic protein–membrane interactions. In this study, we consider four peptide systems with various combinations of flanking sequences (KKQ35KK, KKQ35P11KK, N17Q35KK, N17Q35P11KK) and use atomistic molecular dynamics simulations to study the interactions with a DOPC lipid bilayer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Role of S-turn2 in the Structure, Dynamics, and Function of Mitochondrial Ribosomal A-Site. A Bioinformatics and Molecular Dynamics Simulation Study

Joanna Panecka, Marek Havrila, Kamila Réblová, Jiří Šponer, Joanna Trylska [Masaryk University]

J. Phys. Chem. B., **118**, 6687–6701, 2014.

The mRNA decoding site (A-site) in the small ribosomal subunit controls fidelity of the translation process. Here, using MD simulations and bioinformatic analyses, we investigated the structural dynamics of the human mitochondrial A-site and compared it with the dynamics of the bacterial A-site. We detected and characterized a specific RNA backbone configuration, S-turn2, which occurs in the human mitochondrial but not in the bacterial A-site. Mitochondrial and bacterial A-sites show different propensities to form S-turn2 that may be caused by different base-pairing patterns of the flanking nucleotides.

Lipid-Modified Polyethylenimine-Mediated DNA Attraction Evaluated by Molecular Dynamics Simulations

Sampada Bagai, Chongbo Sun, Tian Tang [University of Alberta]

J. Phys. Chem. B., **118**, 7070–7076, 2014.

The effect of lipid modification on polyethylenimine (PEI)-mediated DNA attraction was studied by performing umbrella sampling molecular dynamics simulations that involved PEIs modified with three different types of lipids: oleic acid (OA), linoleic acid (LA), and caprylic acid (CA). The potential of mean force between two DNA molecules in the presence of these lipid-modified PEIs was calculated using the weighted histogram analysis method, and it predicted the stability and size of the DNA aggregate.

A comparison of various optimization algorithms of protein–ligand docking programs by fitness accuracy

Liyong Guo, Zhiqiang Yan, Xiliang Zheng, Liang Hu, Yongliang Yang, Jin Wang [Chinese Academy of Sciences]

J. Mol.Mod., **20**, 2251, 2014.

In protein–ligand docking, an optimization algorithm is used to find the best binding pose of a ligand against a protein target. This algorithm plays a vital role in determining the docking accuracy. To evaluate the relative performance of different optimization algorithms and provide guidance for real applications, we performed a comparative study on six efficient optimization algorithms, containing two evolutionary algorithm (EA)-based optimizers (LGA, DockDE) and four particle swarm optimization (PSO)-based optimizers (SODock, varCPSO, varCPSO-ls, FIPSDock), which were implemented into the protein–ligand docking program AutoDock.

Protein Folding

Concerted Dihedral Rotations Give Rise to Internal Friction in Unfolded Proteins

Ignacia Echeverria, Dmitrii E. Makarov, Garegin A. Papoian [University of Maryland]

J. Am. Chem. Soc., 2013, **136**, 8708–8713, 2014.

Protein chains undergo conformational diffusion during folding and dynamics, experiencing both thermal kicks and viscous drag. Recent experiments have shown that the corresponding friction can be separated into wet friction, which is determined by the solvent viscosity, and dry friction, where frictional effects arise due to the interactions within the protein chain. Despite important advances, the molecular origins underlying dry friction in proteins have remained unclear. We studied the dynamics of the unfolded cold-shock protein at different solvent viscosities and denaturant concentrations.

Protein Folding (Cont'd)

Folding of Fourteen Small Proteins with a Residue-Specific Force Field and Replica-Exchange Molecular Dynamics

Fan Jiang , Yun-Dong Wu [Peking University]

J. Am. Chem. Soc., 2013, **136**, 9536–9539, 2014.

Ab initio protein folding via physical-based all-atom simulation is still quite challenging. Using a recently developed residue-specific force field (RSFF1) in explicit solvent, we are able to fold a diverse set of 14 model proteins. The obtained structural features of unfolded state are in good agreement with previous observations.

General Mechanism of Two-State Protein Folding Kinetics

Geoffrey C. Rollins , Ken A. Dill [Stony Brook University]

J. Am. Chem. Soc., 2013, **136**, 11420–11427, 2014.

We describe here a general model of the kinetic mechanism of protein folding. In the Foldon Funnel Model, proteins fold in units of secondary structures, which form sequentially along the folding pathway, stabilized by tertiary interactions. The model predicts that the free energy landscape has a volcano shape, rather than a simple funnel, that folding is two-state (single-exponential) when secondary structures are intrinsically unstable, and that each structure along the folding path is a transition state for the previous structure.

Quantifying the Sources of Kinetic Frustration in Folding Simulations of Small Proteins

Andrej J. Savol , Chakra S. Chennubhotla [University of Pittsburgh]

J. Chem. Theor. and Comp, **10**, 2964–2974, 2014.

Experiments and atomistic simulations of polypeptides have revealed structural intermediates that promote or inhibit conformational transitions to the native state during folding. We invoke a concept of “kinetic frustration” to quantify the prevalence and impact of these behaviors on folding rates within a large set of atomistic simulation data for 10 fast-folding proteins, where each protein’s conformational space is represented as a Markov state model of conformational transitions.

Multistage Unfolding of an SH3 Domain: An Initial Urea-Filled Dry Molten Globule Precedes a Wet Molten Globule with Non-Native Structure

Amrita Dasgupta, Jayant B. Udgaonkar [Tata Institute of Fundamental Research], Payel Das

J. Phys. Chem. B., **118**, 6380–6392, 2014.

The unfolding of the SH3 domain of the PI3 kinase in aqueous urea has been studied using a synergistic experiment–simulation approach. The experimental observation of a transient wet molten globule intermediate, IU, with an unusual non-native burial of the sole Trp residue, W53, provides the benchmark for the unfolding simulations performed (eight in total, each at least 0.5 μ s long). The simulations reveal that the partially unfolded IU ensemble is preceded by an early native-like molten globule intermediate ensemble I*.

Filling Up the Heme Pocket Stabilizes Apomyoglobin and Speeds Up Its Folding

J. S. Goodman, S.-H. Chao, T. V. Pogorelov, M. Gruebele [University of Illinois]

J. Phys. Chem. B., **118**, 6511–6518, 2014.

Wild type apomyoglobin folds in at least two steps: the ABGH core rapidly, followed much later by the heme-binding CDEF core. We hypothesize that the evolved heme-binding function of the CDEF core frustrates its folding: it has a smaller contact order and is no more complex topologically than ABGH, and thus, it should be able to fold faster. Therefore, filling up the empty heme cavity of apomyoglobin with larger, hydrophobic side chains should significantly stabilize the protein and increase its folding rate.

Protein Folding (Cont'd)

Hierarchical Folding Free Energy Landscape of HP35 Revealed by Most Probable Path Clustering

Abhinav Jain , Gerhard Stock [Albert Ludwigs University]

J. Phys. Chem. B., **118**, 7750–7760, 2014.

Adopting extensive molecular dynamics simulations of villin headpiece protein (HP35) by Shaw and co-workers, a detailed theoretical analysis of the folding of HP35 is presented. The approach is based on the recently proposed most probable path algorithm which identifies the metastable states of the system, combined with dynamical coring of these states in order to obtain a consistent Markov state model. The method facilitates the construction of a dendrogram associated with the folding free-energy landscape of HP35, which reveals a hierarchical funnel structure and shows that the native state is rather a kinetic trap than a network hub.

Protein-Nucleic acid Interactions

Reaction mechanism of Ru(II) piano-stool complexes: Umbrella sampling QM/MM MD study

Zdeněk Futera ,Jaroslav V. Burda [Charles University in Prague]

J. Comp. Chem., **35**, 1446–1456, 2014.

Biologically relevant interactions of piano-stool ruthenium(II) complexes with ds-DNA are studied in this article by hybrid quantum mechanics—molecular mechanics (QM/MM) computational technique. The whole reaction mechanism is divided into three phases: (i) hydration of the $[\text{Ru}^{\text{II}}(\eta^6\text{-benzene})(\text{en})\text{Cl}]^+$ complex, (ii) monoadduct formation between the resulting aqua-Ru(II) complex and N7 position of one of the guanines in the ds-DNA oligomer, and (iii) formation of the intrastrand Ru(II) bridge (cross-link) between two adjacent guanines.

Structural and Energetic Analysis of 2-Aminobenzimidazole Inhibitors in Complex with the Hepatitis C Virus IRES RNA Using Molecular Dynamics Simulations

Niel M. Henriksen, Hamed S. Hayatshahi, Darrell R. Davis, Thomas E. Cheatham, III [University of Utah]

J.Chem. Infor. and Mod. **54**, 1758–1772, 2014.

Despite the many biological functions of RNA, very few drugs have been designed or found to target RNA. Here we report the results of molecular dynamics (MD) simulations and binding energy analyses on hepatitis C virus internal ribosome entry site (IRES) RNA in complex with highly charged 2-aminobenzimidazole inhibitors. Initial coordinates were taken from NMR and crystallography studies that had yielded different binding modes. During MD simulations, the RNA–inhibitor complex is stable in the crystal conformation but not in the NMR conformation.

Nucleic Acids

Basin Hopping Graph: a computational framework to characterize RNA folding landscapes

Marcel Kucharík, Ivo L. Hofacker, Peter F. Stadler, Jing Qin
[University Of Southern Denmark]

Bioinformatics. **30**, 2009-2017, 2014.

RNA folding is a complicated kinetic process. The minimum free energy structure provides only a static view of the most stable conformational state of the system. It is insufficient to give detailed insights into the dynamic behavior of RNAs. A sufficiently sophisticated analysis of the folding free energy landscape, however, can provide the relevant information. We introduce the Basin Hopping Graph (BHG) as a novel coarse-grained model of folding landscapes. Each vertex of the BHG is a local minimum, which represents the corresponding basin in the landscape.

comTAR: a web tool for the prediction and characterization of conserved microRNA targets in plants

Uciel Chorostecki, Javier F. Palatnik [Universidad Nacional de Rosario]

Bioinformatics. **30**, 2066-2067, 2014.

MicroRNAs (miRNAs) are major regulators of gene expression in plants and animals. They recognize their target messenger RNAs (mRNAs) by sequence complementarity and guide them to cleavage or translational arrest. So far, the prediction of plant miRNA-target pairs generally relies on the use of empirical parameters deduced from known miRNA-target interactions. We developed comTAR, a web tool for the prediction of miRNA targets that is mainly based on the conservation of the potential regulation in different species.

EnsembleGASVR: a novel ensemble method for classifying missense single nucleotide polymorphisms

Trisevgeni Rapakoulia, Konstantinos Theofilatos, Dimitrios Kleftogiannis, Spiros Likothanasis, Athanasios Tsakalidis, Seferina Mavroudi [University of Patras]

Bioinformatics. **30**, 2324-2333, 2014.

Single nucleotide polymorphisms (SNPs) are considered the most frequently occurring DNA sequence variations. Several computational methods have been proposed for the classification of missense SNPs to neutral and disease associated. However, existing computational approaches fail to select relevant features by choosing them arbitrarily without sufficient documentation. To overcome these limitations, a novel ensemble computational methodology is proposed. EnsembleGASVR facilitates a two-step algorithm, which in its first step applies a novel evolutionary embedded algorithm to locate close to optimal Support Vector Regression models.

Temperature effect on poly(dA).poly(dT): molecular dynamics simulation studies of polymeric and oligomeric constructs

Sanchita Mukherjee, Sangeeta Kundu, Dhananjay Bhattacharyya [Saha Institute of Nuclear Physics]

J. Comp. Aided. Mol. Design, **28**, 735-749, 2014.

Understanding unwinding and melting of double helical DNA is very important to characterize role of DNA in replication, transcription, translation etc. Sequence dependent melting thermodynamics is used extensively for detecting promoter regions but melting studies are generally done for short oligonucleotides. This study reports several molecular dynamics (MD) simulations of homopolymeric poly(dA).poly(dT) as regular oligonucleotide fragments as well as its corresponding polymeric constructs with water and charge-neutralizing counterions at different temperatures ranging from 300 to 400 K.

Nucleic Acids (Cont'd)

A Coarse-Grained Model of Unstructured Single-Stranded DNA Derived from Atomistic Simulation and Single-Molecule Experiment

Christopher Maffeo, Thuy T. M. Ngo, Taekjip Ha, Aleksei Aksimentiev [University of Illinois at Urbana–Champaign]

J. Chem. Theor. and Comp., **10**, 2891–2896, 2014.

A simple coarse-grained model of single-stranded DNA (ssDNA) was developed, featuring only two sites per nucleotide that represent the centers of mass of the backbone and sugar/base groups. In the model, the interactions between sites are described using tabulated bonded potentials optimized to reproduce the solution structure of DNA observed in atomistic molecular dynamics simulations. Isotropic potentials describe nonbonded interactions, implicitly taking into account the solvent conditions to match the experimentally determined radius of gyration of ssDNA. The model reproduces experimentally measured force–extension dependence of an unstructured DNA strand across 2 orders of magnitude of the applied force.

Base Pair Fraying in Molecular Dynamics Simulations of DNA and RNA

Marie Zgarbová, Michal Otyepka, Jiří Šponer, Filip Lankaš, Petr Jurečka [Palacky University]

J. Chem. Theor. and Comp., **10**, 3177–3189, 2014.

Terminal base pairs of DNA and RNA molecules in solution are known to undergo frequent transient opening events (fraying). Accurate modeling of this process is important because of its involvement in nucleic acid end recognition and enzymatic catalysis. In this article, we describe fraying in MD simulations with the ff99bsc0, ff99bsc0χOL3, and ff99bsc0χOL4 force fields, both for DNA and RNA molecules. Comparison with the experiment showed that while some features of fraying are consistent with the available data, others indicate potential problems with the force field description.

Elucidating the Relation between Internal Motions and Dihedral Angles in an RNA Hairpin Using Molecular Dynamics

Alok Juneja, Alessandra Villa, Lennart Nilsson [Karolinska Institutet]

J. Chem. Theor. and Comp., **10**, 3532–3540, 2014.

Molecular dynamics simulations were performed to characterize the internal motions of the ribonucleic acid apical stem loop of human hepatitis B virus. The NMR relaxation rates calculated directly from the trajectory are in good agreement with the experiment. Calculated order parameters follow the experimental pattern. Order parameters lower than 0.8 are observed for nucleotides that are weakly hydrogen bonded to their base pair partner, unpaired, or part of the loop. These residues show slow decay of the internal correlation functions of their base and sugar C–H vectors. Concerted motions around backbone dihedral angles influence the amplitude of motion of the sugar and base C–H vectors.

A Solvent-Mediated Coarse-Grained Model of DNA Derived with the Systematic Newton Inversion Method

Aymeric Naômé [University of Namur], Aatto Laaksonen, Daniel P. Vercauteren

J. Chem. Theor. and Comp., **10**, 3541–3549, 2014.

We present a new class of coarse-grained (CG) force fields (FFs) for B-DNA with explicit ions suited for large-scale mesoscale simulations at microsecond–micrometer scale using a wide spectrum of particle simulation methods from molecular dynamics to dissipative particle dynamics. The effective solvent-mediated pairwise interactions making up the FFs are obtained by inverting radial distribution functions and other particle–particle distributions obtained from all-atom simulations of numbers of octadecamer DNA fragments from the Ascona B-DNA library.

Nucleic Acids (Cont'd)

Interdomain communication in the endonuclease/motor subunit of type I restriction-modification enzyme EcoR124I

Dhiraj Sinha, Katsiaryna Shamayeve, Vyas Ramasubramani, David Řeha, Vitali Bialeovich, Morteza Khabiri, Alena Guzanová, Niv Milbar, Marie Weiserová, Eva Csefalvay, Jannette Carey, Rüdiger Ettrich [Academy of Sciences of the Czech Republic]

J. Mol.Mod., **20**, 2334, 2014.

Restriction-modification systems protect bacteria from foreign DNA. Type I restriction-modification enzymes are multifunctional heteromeric complexes with DNA-cleavage and ATP-dependent DNA translocation activities located on endonuclease/motor subunit HsdR. In the present work, molecular dynamics simulations are used to explore this proposal. Molecular dynamics simulations suggest that the Lys-ATP contact alternates with a contact with a nearby loop housing the conserved QxxxY motif that had been implicated in DNA cleavage. This model is tested here using in vivo and in vitro experiments.

Surfaces, Catalysts, and Materials Subjects

Molecular Mechanism of Selective Binding of Peptides to Silicon Surface

Sathish Kumar Ramakrishnan, Marta Martin, Thierry Cloitre, Lucyna Firlej, Csilla Gergely [Université Montpellier 2]

J.Chem. Infor. and Mod. **54**, 2117–2126, 2014.

Despite extensive recent research efforts on material-specific peptides, the fundamental problem to be explored yet is the molecular interactions between peptides and inorganic surfaces. Here we used computer simulations (density functional theory and classical molecular dynamics) to investigate the adsorption mechanism of silicon-binding peptides and the role of individual amino acids in the affinity of peptides for an n-type silicon (n+-Si) semiconductor. T

2. METHODOLOGY

Potentials and Parameters

Empirical Maps For The Calculation of Amide I Vibrational Spectra of Proteins From Classical Molecular Dynamics Simulations

Edyta Małolepsza, John E. Straub [Boston University]

J. Phys. Chem. B., **118**, 7848–7855, 2014.

New sets of parameters (maps) for calculating amide I vibrational spectra for proteins through a vibrational exciton model are proposed. The maps are calculated as a function of electric field and van der Waals forces on the atoms of peptide bonds, taking into account the full interaction between peptide bonds and the surrounding environment. The maps are designed to be employed using data obtained from standard all-atom molecular simulations without any additional constraints on the system. Six proteins representing a wide range of sizes and secondary structure complexity were chosen as a test set. Spectra calculated for these proteins reproduce experimental data both qualitatively and quantitatively.

Molecular Dynamics

Kinetic modelling of mitochondrial translation

Kalyani Korla, Chanchal K. Mitra [University of Hyderabad]

J. Biomol. Stru. and Dyn., 32, 1634-1650, 2014.

Mitochondrial genome contains 13 protein coding genes, all being part of the oxidative phosphorylation complexes. The process of translation of these protein coding mRNAs in mitochondrial matrix is a good miniature model of translation in cytoplasm. In this work, we have simulated three phases of mitochondrial translation viz. initiation, elongation and termination (including ribosome recycling). The kinetic equations for these phases have been deduced based on the information available in literature. Various factors involved in the process have been included explicitly.

Atom Pair 2D-Fingerprints Perceive 3D-Molecular Shape and Pharmacophores for Very Fast Virtual Screening of ZINC and GDB-17

Mahendra Awale , Jean-Louis Reymond [University of Berne]

J.Chem. Infor. and Mod. **54**, 1892–1907, 2014.

Three-dimensional (3D) molecular shape and pharmacophores are important determinants of the biological activity of organic molecules; however, a precise computation of 3D-shape is generally too slow for virtual screening of very large databases. A reinvestigation of the concept of atom pairs initially reported by Carhart et al. and extended by Schneider et al. showed that a simple atom pair fingerprint (APfp) counting atom pairs at increasing topological distances in 2D-structures without atom property assignment correlates with various representations of molecular shape extracted from the 3D-structures.

Three-Dimensional Brownian Dynamics Simulator for the Study of Ion Permeation through Membrane Pores

Claudio Berti [Rush University Medical Center], Simone Furini, Dirk Gillespie, Dezső Boda, Robert S. Eisenberg, Enrico Sangiorgi, Claudio Fiegna

J. Chem. Theor. and Comp., **10**, 2911–2926, 2014.

A three-dimensional numerical simulator based on Brownian dynamics (BD) for the study of ion transport through membrane pores is presented. Published BD implementations suffer from severe shortcomings in accuracy and efficiency. Here, we introduce a new BD simulator in which these critical issues are addressed, implementing advanced techniques: (i) unphysical ion configurations are managed with a novel retracing technique; (ii) ion motion is evaluated integrating the Langevin equation with the algorithm of van Gunsteren and Berendsen (Mol. Phys. 1982, 45, 637–647); (iii) dielectric response in the Poisson equation is solved at run time with the Induced Charge Computation (ICC) method of Boda et al.

Lipoic Acid and Dihydrolipoic Acid. A Comprehensive Theoretical Study of Their Antioxidant Activity Supported by Available Experimental Kinetic Data

Romina Castañeda-Arriaga , J. Raul Alvarez-Idaboy [Universidad Nacional Autonoma de Mexico]

J.Chem. Infor. and Mod. **54**, 1642–1652, 2014.

The free radical scavenging activity of lipoic acid (LA) and dihydrolipoic acid (DHLA) has been studied in nonpolar and aqueous solutions, using the density functional theory and several oxygen centered radicals. It was found that lipoic acid is capable of scavenging only very reactive radicals, while the dehydrogenated form is an excellent scavenger via a hydrogen transfer mechanism. The environment plays an important role in the free radical scavenging activity of DHLA because in water it is deprotonated, and this enhances its activity.

Molecular Dynamics (Cont'd)

Sodium binding to hH₃R and hH₄R — a molecular modeling study

Hans-Joachim Wittmann, Roland Seifert, Andrea Strasser [University of Regensburg]

J. Mol.Mod., **20**, 2394, 2014.

Several aminergic GPCRs, e.g., the human histamine H₃-receptor (hH₃R) are sensitive to sodium ions. Based on these experimental results, including site directed mutagenesis studies, a sodium binding pocket near to the highly conserved Asp^{2.50} was suggested. Recently, in the crystallized adenosine A_{2A} receptor (4EIY), a sodium ion was found in a pocket, coordinated by Asp⁵², Ser⁹¹, and three water molecules. Despite high homology in amino acid sequence between hH₃R and hH₄R, pharmacological studies revealed that the hH₄R is — in contrast to hH₃R — not sensitive to sodium ions.

Free Energy Perturbation

Box size effects are negligible for solvation free energies of neutral solutes

Sreeja Parameswaran, David L. Mobley [University of California]

J. Comp. Aided. Mol. Design, **28**, 825-829, 2014.

Hydration free energy calculations in explicit solvent have become an integral part of binding free energy calculations and a valuable test of force fields. We examine whether similar size-dependence affects hydration of neutral molecules. Thus, we focused on two strongly polar molecules with large dipole moments, where any size-dependence should be most pronounced, and determined how their hydration free energies vary as a function of simulation box size. In addition to testing a variety of simulation box sizes, we also tested two LJ cut-off distances, 0.65 and 1.0 nm.

QM and QM/MM

Differential Control of Heme Reactivity in Alpha and Beta Subunits of Hemoglobin: A Combined Raman Spectroscopic and Computational Study

Eric M. Jones, Emanuele Monza, Gurusamy Balakrishnan, George C. Blouin, Piotr J. Mak, Qianhong Zhu, James R. Kincaid, Victor Guallar, Thomas G. Spiro [University of Washington]

J. Am. Chem. Soc., 2013, **136**, 10325–10339, 2014.

The use of hybrid hemoglobin (Hb), with mesoheme substituted for protoheme, allows separate monitoring of the α or β hemes along the allosteric pathway. Using resonance Raman (rR) spectroscopy in silica gel, which greatly slows protein motions, we have observed that the Fe–histidine stretching frequency, ν_{FeHis} , which is a monitor of heme reactivity, evolves between frequencies characteristic of the R and T states, for both α or β chains, prior to the quaternary R–T and T–R shifts. Computation of ν_{FeHis} , using QM/MM and the conformational search program PELE, produced remarkable agreement with experiment.

QM and QM/MM (Cont'd)

Multiscale Reactive Molecular Dynamics for Absolute pKa Predictions and Amino Acid Deprotonation

J. Gard Nelson, Yuxing Peng, Daniel W. Silverstein, Jessica M. J. Swanson [University of Chicago]

J. Chem. Theor. and Comp., **10**, 2729–2737, 2014.

Accurately calculating a weak acid's pKa from simulations remains a challenging task. We report a multiscale theoretical approach to calculate the free energy profile for acid ionization, resulting in accurate absolute pKa values in addition to insights into the underlying mechanism. Importantly, our approach minimizes empiricism by mapping electronic structure data (QM/MM forces) into a reactive molecular dynamics model capable of extensive sampling. Consequently, the bulk property of interest (the absolute pKa) is the natural consequence of the model, not a parameter used to fit it.

Computing the Free Energy Barriers for Less by Sampling with a Coarse Reference Potential while Retaining Accuracy of the Target Fine Model

Nikolay V. Plotnikov [Stanford University]

J. Chem. Theor. and Comp., **10**, 2987–3001, 2014.

Proposed in this contribution is a protocol for calculating fine-physics (e.g., ab initio QM/MM) free-energy surfaces at a high level of accuracy locally (e.g., only at reactants and at the transition state for computing the activation barrier) from targeted fine-physics sampling and extensive exploratory coarse-physics sampling. The full free-energy surface is still computed but at a lower level of accuracy from coarse-physics sampling. The method is analytically derived in terms of the umbrella sampling and the free-energy perturbation methods which are combined with the thermodynamic cycle and the targeted sampling strategy of the paradynamics approach.

Reaction Path Force Matching: A New Strategy of Fitting Specific Reaction Parameters for Semiempirical Methods in Combined QM/MM Simulations

Yan Zhou, Jingzhi Pu [Indiana University-Purdue University Indianapolis]

J. Chem. Theor. and Comp., **10**, 3038–3054, 2014.

We present a general strategy of reparametrizing semiempirical (SE) methods against ab initio (AI) methods for combined quantum mechanical and molecular mechanical (QM/MM) simulations of specific chemical reactions in condensed phases. The resulting approach, designated Reaction Path Force Matching (RP-FM), features cycles of sampling configurations along a reaction path on an efficient SE/MM potential energy surface (PES) and adjusting specific reaction parameters (SRPs) in the SE method such that the atomic forces computed at the target AI/MM level are reproduced.

Raman Optical Activity of a Cyclic Dipeptide Analyzed by Quantum Chemical Calculations Combined with Molecular Dynamics Simulations

Hiroyasu Urago, Torao Suga, Taiki Hirata, Hiroaki Kodama, Masashi Unno [Saga University]

J. Phys. Chem. B., **118**, 6767–6774, 2014.

Raman optical activity (ROA) measures the different intensity of right- and left-circularly polarized Raman scattered light and provides information on chirality associated with vibrational modes. Because of a high sensitivity to subtle structural and environmental changes, interpretations of ROA spectra usually rely on quantum chemical simulations. Recent advances in computational chemistry allow us to consider explicit solvent models that are derived from molecular dynamics (MD) simulations to compute the Raman and ROA spectra. An important concern for the explicit solvent models is the number of MD snapshots that lead to a good agreement between the observed and calculated spectra.

QM and QM/MM (Cont'd)

Conductance Simulation of the Purinergic P2X2, P2X4, and P2X7 Ionic Channels Using a Combined Brownian Dynamics and Molecular Dynamics Approach

Dmitry A. Turchenkov [University of Aveiro] , Vladimir S. Bystrov

J. Phys. Chem. B., **118**, 9119–9127, 2014.

This paper investigates the application of an original combined approach of molecular and Brownian dynamic methods with quantum chemistry calculations for modeling the process of conductance of ion channels using purinergic P2X family receptors P2X2, P2X4, and P2X7 as a case study. A simplified model of the ionic channel in the lipid bilayer has been developed. A high level of conductance (30 pS) of P2X2 ionic channel together with the key role of Asp349 in forming the selectivity filter of P2X2 has been shown by using this approach.

Mechanistic insights into the catalytic reaction of plant allene oxide synthase (pAOS) via QM and QM/MM calculations

Tuanjai Somboon, Jun Ochiai, Wittha Treesuwan, M. Paul Gleeson, Supa Hannongbua [Kasetsart University], Seiji Mori

J. Mol.Graph. and Mod., **52**, 20-29, 2014.

QM cluster and QM/MM protein models have been employed to understand aspects of the reaction mechanism of plant allene oxide synthase (pAOS). In this study we have investigated two reaction mechanisms for pAOS. The standard pAOS mechanism was contrasted with an alternative involving an additional active site molecule which has been shown to facilitate proton coupled electron transfer (PCET) in related systems. Firstly, we found that the results from QM/MM protein model are comparable with those from the QM cluster model, presumably due to the large active site used.

Comparative or Homology Modeling

Impact of Template Choice on Homology Model Efficiency in Virtual Screening

Krzysztof Rataj, Jagna Witek, Stefan Mordalski, Tomasz Kosciolk, Andrzej J. Bojarski [Polish Academy of Sciences]

J.Chem. Infor. and Mod. **54**, 1661–1668, 2014.

Homology modeling is a reliable method of predicting the three-dimensional structures of proteins that lack NMR or X-ray crystallographic data. It employs the assumption that a structural resemblance exists between closely related proteins. Despite the availability of many crystal structures of possible templates, only the closest ones are chosen for homology modeling purposes. To validate the aforementioned approach, we performed homology modeling of four serotonin receptors (5-HT1AR, 5-HT2AR, 5-HT6R, 5-HT7R) for virtual screening purposes, using 10 available G-Protein Coupled Receptors (GPCR) templates with diverse evolutionary distances to the targets, with various approaches to alignment construction and model building.

Ligand Docking

Selecting an Optimal Number of Binding Site Waters To Improve Virtual Screening Enrichments Against the Adenosine A2A Receptor

Eelke B. Lenselink, Thijs Beuming, Woody Sherman, Herman W. T. van Vlijmen, Adriaan P. IJzerman [Leiden University]

J.Chem. Infor. and Mod. **54**, 1737–1746, 2014.

A major challenge in structure-based virtual screening (VS) involves the treatment of explicit water molecules during docking in order to improve the enrichment of active compounds over decoys. Here we have investigated this in the context of the adenosine A2A receptor, where water molecules have previously been shown to be important for achieving high enrichment rates with docking, and where the positions of some binding site waters are known from a high-resolution crystal structure.

g_mmpbsa—A GROMACS Tool for High-Throughput MM-PBSA Calculations

Rashmi Kumari, Rajendra Kumar, Open Source Drug Discovery Consortium, Andrew Lynn [Jawaharlal Nehru University]

J.Chem. Infor. and Mod. **54**, 1951–1962, 2014.

Molecular mechanics Poisson–Boltzmann surface area (MM-PBSA), a method to estimate interaction free energies, has been increasingly used in the study of biomolecular interactions. Recently, this method has also been applied as a scoring function in computational drug design. Here a new tool *g_mmpbsa*, which implements the MM-PBSA approach using subroutines written in-house or sourced from the GROMACS and APBS packages is described. *g_mmpbsa* was developed as part of the Open Source Drug Discovery (OSDD) consortium. Its aim is to integrate high-throughput molecular dynamics (MD) simulations with binding energy calculations.

Evaluation and Application of MD-PB/SA in Structure-Based Hierarchical Virtual Screening

Ran Cao, Niu Huang, Yanli Wang [National Institute of Biological Sciences, Beijing]

J.Chem. Infor. and Mod. **54**, 1987–1996, 2014.

Molecular dynamics (MD) based molecular mechanics Poisson–Boltzmann and surface area (MM-PB/SA) calculation (MD-PB/SA) has been widely used to estimate binding free energies for receptor–ligand complexes. While numerous reports have focused on assessing accuracy and efficiency, fewer studies have paid attention to performance in lead discovery. In the present study, we report a critical evaluation of MD-PB/SA in hierarchical virtual screening (HVS) both theoretically and practically.

Allosteric pocket of the dengue virus (serotype 2) NS2B/NS3 protease: In silico ligand screening and molecular dynamics studies of inhibition

Azat Mukhametov [Universiti Sains Malaysia], E. Irene Newhouse, Nurohaida Ab Aziz, Jennifer A. Saito, Maqsudul Alam

J. Mol.Graph. and Mod., **52**, 103–113, 2014.

The allosteric pocket of the Dengue virus (DENV2) NS2B/NS3 protease, which is proximal to its catalytic triad, represents a promising drug target (Othman et al., 2008). We have explored this binding site through large-scale virtual screening and molecular dynamics simulations followed by calculations of binding free energy. We propose two mechanisms for enzyme inhibition. A ligand may either destabilize electronic density or create steric effects relating to the catalytic triad residues NS3-HIS51, NS3-ASP75, and NS3-SER135. A ligand may also disrupt movement of the C-terminal of NS2B required for inter-conversion between the “open” and “closed” conformations.

Ligand Docking (Cont'd)

Effective Virtual Screening Strategy toward Covalent Ligands: Identification of Novel NEDD8-Activating Enzyme Inhibitors

Shengping Zhang, Jiani Tan, Zhonghui Lai, Ying Li, Junxia Pang, Jianhu Xiao, Zhangjian Huang, Yihua Zhang, Hui Ji, Yisheng Lai [China Pharmaceutical University]

J.Chem. Infor. and Mod. **54**, 1785–1797, 2014.

The NEDD8-activating enzyme (NAE) is an emerging target for cancer therapy, which regulates the degradation and turnover of a variety of cancer-related proteins by activating the cullin-RING E3 ubiquitin ligases. Among a limited number of known NAE inhibitors, the covalent inhibitors have demonstrated the most potent efficacy through their covalently linked adducts with NEDD8. Inspired by this unique mechanism, in this study, a novel combined strategy of virtual screening (VS) was adopted with the aim to identify diverse covalent inhibitors of NAE.

Computational Prediction of a Putative Binding Site on Drp1: Implications for Antiparkinsonian Therapy

Hanumanthappa Pradeep , G. Krishnamurthy Rajanikant [National Institute of Technology Calicut]

J.Chem. Infor. and Mod. **54**, 2042–2050, 2014.

Parkinson's disease is the second most common neurodegenerative disorder, for which no cure or disease-modifying therapies exist. It is evident that mechanisms impairing mitochondrial dynamics will damage cell signaling pathways, leading to neuronal death that manifests as Parkinson's disease. Dynamin related protein1, a highly conserved proffission protein that catalyzes the process of mitochondrial fission, is also associated with the excessive fragmentation of mitochondria, impaired mitochondrial dynamics and cell death.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 52, July, 2014.

- 1-10 **Constrained geometric simulation of the nicotinic acetylcholine receptor** ,William J. Belfield, Daniel J. Cole, Ian L. Martin, Mike C. Payne, P.-L. Chau[Institut Pasteur]

Constrained geometric simulations have been performed for the recently published closed-channel state of the nicotinic acetylcholine receptor.

- 11-19 **Homology modelling, docking, pharmacophore and site directed mutagenesis analysis to identify the critical amino acid residue of PknI from Mycobacterium tuberculosis** ,Srinivasan Kandasamy, Sameer Hassan, Radha Gopalaswamy, Sujatha Narayanan[National Institute for Research in Tuberculosis (NIRT) (ICMR)]

See Applications / Medicinal Chemistry and Drug Design.

- 20-29 **Mechanistic insights into the catalytic reaction of plant allene oxide synthase (pAOS) via QM and QM/MM calculations** ,Tuanjai Somboon, Jun Ochiai, Witcha Treesuwan, M. Paul Gleeson, Supa Hannongbua [Kasetsart University], Seiji Mori

See Methodology / QM and QM/MM.

- 30-35 **Trends in predicted chemoselectivity of cytochrome P450 oxidation: B3LYP barrier heights for epoxidation and hydroxylation reactions** ,Patrik Rydberg, Richard Lonsdale, Jeremy N. Harvey, Adrian J. Mulholland, Lars Olsen[University of Copenhagen]

Prediction of epoxide formation in drug metabolism is a difficult but important task, as epoxide formation is linked to drug toxicity. A comparison of the energy barriers for cytochrome P450 mediated epoxidation of alkenes to the barriers for the hydroxylation of an aliphatic carbon atom next to a double bond has been performed using B3LYP and B3LYP-D3.

- 36-45 **Theoretical prediction of structural, vibrational and NMR parameters of plastic optical fiber (POF) material precursors. Cis and trans perhydro- and perfluoro-2-methylene-4,5-dimethyl-1,3-dioxolanes** ,Farhod Nozirov, Teobald Kupka [Opole University], Michał Stachów

Density functional theory (DFT) prediction of cis and trans perhydro- and perfluoro-2-methylene-4,5-dimethyl-1,3-dioxolanes structure, supported by vibrational analysis and calculation of multinuclear isotropic nuclear magnetic resonance (NMR) shieldings and indirect spin-spin couplings (SSCCs) was performed.

- 46-56 **Structure-based drug design of small molecule SIRT1 modulators to treat cancer and metabolic disorders** ,Venkat Koushik Pulla, Mallika Alvala, Dinavahi Saketh Sriram, Srikant Viswanadha, Dharmarajan Sriram, Perumal Yogeewari[Birla Institute of Technology & Science-Pilani]

Sirtuins comprise a family of deacetylase enzymes that catalyze the removal of an acetyl moiety from the ϵ -amino group of lysine residues within protein targets. Sirtuin 1(SIRT1), a NAD^+ dependent class III histone

deacetylase is involved in a variety of human disorders such as obesity, type II diabetes, cancer and aging. . In this paper, we report diverse small molecule inhibitors with a potential to attenuate cancer growth designed based on high-throughput virtual screening and docking using the crystal structure of SIRT1.

- 57-70 **Identification of the transition state for fast reactions: The trapping of hydroxyl and methyl radicals by DMPO—A DFT approach** ,Benjamín Aguilera-Venegas [University of Chile], Hernán Speisky

Up to date, attempts to locate the transition state (TS) for the trapping reaction between $\bullet\text{OH}$ and DMPO have been unsuccessful, and the lack of molecular mechanisms by which $\bullet\text{OH}$ binds to the spin-trap constitutes a question still unsolved. Herein, we have taken a step forward on this task by describing the theoretical TS for the trapping of $\bullet\text{OH}$ and $\bullet\text{CH}_3$ by DMPO and the intrinsic reaction coordinates.

- 71-81 **A DFT study on the physical adsorption of cyclophosphamide derivatives on the surface of fullerene C_{60} nanocage** ,Zahra Shariatinia [Amirkabir University of Technology], Samira Shahidi

The physical sorption of a series of cyclophosphamide drug derivatives with formula $[\text{NH}(\text{CH}_2)_3\text{O}]\text{P}(\text{O})(\text{N}[(\text{CH}_2)_x\text{X}]_2)$ where $x = 2$, $\text{X} = \text{F}$ (2), Cl (3), Br (4); $x = 3$, $\text{X} = \text{F}$ (5), Cl (6), Br (7) and $x = 4$, $\text{X} = \text{F}$ (8), Cl (9), Br (10) on the surface of fullerene C_{60} was studied using density functional theory (DFT) at B3LYP and B3PW91 levels.

- 82-90 **Development of a receptor model for efficient in silico screening of HIV-1 integrase inhibitors** ,Mario A. Quevedo [Universidad Nacional de Córdoba] , Sergio R. Ribone, Margarita C. Briñón, Wim Dehaen

Integrase (IN) is a key viral enzyme for the replication of the type-1 human immunodeficiency virus (HIV-1), and as such constitutes a relevant therapeutic target for the development of anti-HIV agents. In this study, four HIV-1 IN homology models were evaluated respect to their capability to predict the inhibition potency of a training set comprising 36 previously reported INIs with IC_{50} values in the low nanomolar to the high micromolar range.

- 91-102 **The conformational behavior, geometry and energy parameters of Menshutkin-like reaction of O-isopropylidene-protected glycofuranoid mesylates in view of DFT calculations** ,Andrzej Nowacki [University of Gdańsk], Justyna Wielińska, Dominik Walczak, Karol Sikora, Barbara Dmochowska, Beata Liberek

The formation of pyridinium salts in the transformation of three O-isopropylidene-protected mesylates of furanoid sugar derivatives under pyridine action is considered at the B3LYP/6-31+G** computation level.

- 103-113 **Allosteric pocket of the dengue virus (serotype 2) NS2B/NS3 protease: In silico ligand screening and molecular dynamics studies of inhibition** ,Azat Mukhametov [Universiti Sains Malaysia], E. Irene Newhouse, Nurohaida Ab Aziz, Jennifer A. Saito, Maqsudul Alam

See Methodology / Ligand Docking.

- 114-123 **Protein tyrosine phosphatases: Ligand interaction analysis and optimisation of virtual screening** ,Mohammad A. Ghattas, Noor Atatreh, Elena V. Bichenkova, Richard A. Bryce [University of Manchester]

See Methodology / Ligand Docking.

Journal of Molecular Modeling, 20 (7), July, 2014.

- 2358 **Structural and functional alterations of myoglobin by glucose-protein interactions** ,Yong You, Fang Liu, Ke-Jie Du, Ge-Bo Wen [University of South China], Ying-Wu Lin

See Applications / Ligand Binding.

- 2350 **Pressure-induced metallization of condensed phase β -HMX under shock loadings via molecular dynamics simulations in conjunction with multi-scale shock technique** , Ni-Na Ge, Yong-Kai Wei, Feng Zhao, Xiang-Rong Chen[Sichuan University], Guang-Fu Ji

The electronic structure and initial decomposition in high explosive HMX under conditions of shock loading are examined. The simulation is performed using quantum molecular dynamics in conjunction with multi-scale shock technique (MSST). A self-consistent charge density-functional tight-binding (SCC-DFTB) method is adapted.

- 2348 **Induced fit docking, pharmacophore modeling, and molecular dynamic simulations on thiazolidinedione derivatives to explore key interactions with Tyr48 in polyol pathway** ,Manga Vijjulatha [Osmania University], Yamini Lingala, RaviRaja Tejaswi Merugu

See Applications / Homology Modeling.

- 2347 **Understanding the domino retro [3+2] cycloaddition/cyclization reaction of bicyclic isoxazolidines in the synthesis of spirocyclic alkaloids. A DFT study** ,Hatem Layeb, Abdelmalek Khorief Nacereddine, Abdelhafid Djerourou, Luis R. Domingo [domingo@utopia.uv.es]

The domino retro [3+2] cycloaddition/cyclization reaction of bicyclic isoxazolidines **4** yielding [6.6.5]-tricyclic isoxazolidines **7** and [6.5.5]-tricyclic isoxazolidines **8**, experimentally reported by Holmes et al., has been studied in toluene using DFT methods at the MPWB1K/6-311G** level.

- 2346 **Modeling the selectivity of indoor pollution gases over N₂ on covalent organic frameworks** ,Wenliang Li, Yujia Pang, Jingping Zhang [Northeast Normal University]

The selectivity of indoor pollution gases (including formaldehyde, benzene, and toluene) over N₂ on a set of 37 covalent organic frameworks (COFs) was modeled by combining classical grand canonical Monte Carlo (GCMC) methods and periodic density functional theory with dispersion correction (DFT-D2).

- 2345 **Influence of different free radicals on scavenging potency of gallic acid** ,Jelena Đorović [Bioengineering Research and Development Center], Jasmina M. Dimitrić Marković, Višnja Stepanić, Nebojša Begović, Dragan Amić,Zoran Marković

The M05-2X/6-311++G(d,p) and B3LYP-D2/6-311++G(d,p) models are used to evaluate scavenging potency of gallic acid.

- 2344 **Computational and experimental studies on the triplet states of various N-substituted 4,5,6,7-tetrachlorophthalimides** , Anne-Marie Kelterer [Graz University of Technology], Asim Mansha, Faiza Jan Iftikhar, Yan Zhang, Wei Wang, Jian-Hua Xu, Günter Grampp

The triplet-triplet absorption spectra of three newly synthesized N-substituted 4,5,6,7-tetrachlorophthalimides (TCP) were measured experimentally and calculated with density functional theory. The heavy atom effect increases the intersystem crossing rate, and the transient triplet absorbance could be measured.

- 2343 **Theoretical study on the structure and stability of [1,2,5] oxadiazolo [3,4-e] [1,2,3,4]-tetrazine-4,6-Di-N-dioxide (FTDO)** , Wei-Peng Lai [Xi'an modern chemistry research institute], Peng Lian, Tao Yu, Jian-Hua Bu, Ying-Zhe Liu, Wei-Liang Zhu, Jian Lv, Zhong-Xue GE

Although many 1,2,3,4-tetrazine-1,3-dioxide derivatives have been synthesized, [1,2,5] oxadiazolo [3,4-e] [1,2,3,4]-tetrazine-4,6-di-N-dioxide (FTDO) is the only one with high enthalpy of formation and high detonation velocity.

- 2341 **A B3LYP and MP2(full) theoretical investigation into cooperativity effects, aromaticity and thermodynamic properties in the $\text{Na}^+\cdots\text{benzonitrile}\cdots\text{H}_2\text{O}$ ternary complex** , Guang-ming Zhao, Yu-cun Liu, Wen-jing Shi, Tao Chai, Fu-de Ren [North University of China]

The cooperativity effects between H-bonding and $\text{Na}^+\cdots\pi$ or $\text{Na}^+\cdots\sigma$ interactions in $\text{Na}^+\cdots\text{benzonitrile}\cdots\text{H}_2\text{O}$ complexes were investigated using the B3LYP and MP2(full) methods with 6-311++G(2d,p) and aug-cc-pVTZ basis sets.

- 2340 **Homology modeling and protein engineering of alkane monooxygenase in *Burkholderia thailandensis* MSMB121: in silico insights** , Chakresh Kumar Jain [Jaypee Institute of Information Technology], Money Gupta, Yamuna Prasad, Gulshan Wadhwa, Sanjeev Kumar Sharma

The degradation of hydrocarbons plays an important role in the eco-balancing of petroleum products, pesticides and other toxic products in the environment. The degradation of hydrocarbons by microbes such as *Geobacillus thermodenitrificans*, *Burkholderia*, *Gordonia* sp. and *Acinetobacter* sp. has been studied intensively in the literature.

- 2339 ***In silico* identification, structural characterization, and phylogenetic analysis of MdesDEF-2: a novel defensin from the Hessian fly, *Mayetiola destructor*** , William F. Porto, Guilherme M. Fensterseifer, Octavio L. Franco [Universidade Católica de Brasília]

The CS α defensins are one of the most ancient antimicrobial peptide classes and are distributed in plants, invertebrates, and fungi. In the insect immunity, the defensins play a crucial role in protection against pathogens. Here, a novel defensin, MdesDEF-2, was identified from the model insect *Mayetiola destructor*, the most destructive insect pest of wheat worldwide. The *in silico* identification of MdesDEF-2 was done through searching by regular expression in *M. destructor*'s protein sequences available at NCBI.

- 2337 **Evaluation of the antiradical activity of hyperjovanol-A utilizing donor-acceptor maps** , Rogelio A. Delgado Alfaro, Zeferino Gomez-Sandoval, Liliana Mammino [University of Venda]

Hyperjovanol-A ((2-methyl-1-(2,4,6-trihydroxy-3-(3-hydroxy-3,7-dimethyloct-6-enyl)phenyl)propan-1-one) is an acylated phloroglucinol isolated from *Hypericum Jovis* and exhibiting good antioxidant activity. The study investigates the compound's antiradical ability on the basis of the electron-donor and electron-acceptor

abilities of its conformers, deriving donor and acceptor indexes and mapping them in terms of donor-acceptor maps (DAM). The DAMs of vitamins C and E and of carotene astaxanthine are used as comparison references.

- 2336 **A DFT study on the adsorption of benzodiazepines to vermiculite surfaces** , A. J. Palace Carvalho [University of Évora], A. V. Dordio, J. P. Prates Ramalho

Widespread use of pharmaceuticals such as benzodiazepines has been resulting over the last decades in the dissemination of residues of these compounds in the environment, and such fact has been raising increasing concern. In the present study, quantum chemical calculations have been performed by periodic DFT using the projector augmented-wave (PAW) method to characterize the interactions of two benzodiazepine molecules, alprazolam and diazepam, with a surface of clay mineral, vermiculite.

- 2335 **The mechanistic study of the hydroxyl radical reaction with *trans*-2-chlorovinylidichloroarsine** , Wanqiao Zhang[Northeast Normal University], Xiaodi Guo, Yunju Zhang, Fang Wang, Haijie Shi, Jingping Zhang, Rongshun Wang, Shuwei Tang, Haitao Wang, Hao Sun

The *trans*-2-chlorovinylidichloroarsine (Lewisite) was produced and handled during WWI and WWII as chemical warfare agents. In this paper, the gas phase reaction mechanisms of OH radical with *trans*-2-chlorovinylidichloroarsine (lewisite) were studied by second-order Møller–Plesset perturbation theory (MP2) method.

- 2334 **Interdomain communication in the endonuclease/motor subunit of type I restriction-modification enzyme EcoR124I** , Dhiraj Sinha, Katsiaryna Shamayeva, Vyas Ramasubramani, David Řeha, Vitali Bialevich, Morteza Khabiri, Alena Guzanová, Niv Milbar, Marie Weiserová, Eva Csefalvay, Jannette Carey, Rüdiger Ettrich [Academy of Sciences of the Czech Republic]

See Applications / Nucleic Acids.

- 2333 **Core–valence correlation effects on IR calculations: the BF₃ and BCl₃ cases** ,Wagner E. Richter, Arnaldo F. Silva, Luciano N. Vidal, Pedro A. M. Vazquez, Roy E. Bruns [Universidade Estadual de Campinas]

The first theoretical results of core–valence correlation effects are presented for the infrared wavenumbers and intensities of the BF₃ and BCl₃ molecules, using (double– and triple–zeta) Dunning core–valence basis sets at the CCSD(T) level.

- 2332 **Effects of the protonation state in the interaction of an HIV-1 reverse transcriptase (RT) amino acid, Lys101, and a non nucleoside RT inhibitor, GW420867X** , Sérgio E. Galembeck [Departamento de Química], F. Matthias Bickelhaupt, Célia Fonseca Guerra, Eduardo Galembeck

See Applications / Ligand Binding.

- 2330 **Binding-competent states for L-arginine in *E. coli* arginine repressor apoprotein** , Saurabh Kumar Pandey, David Řeha, Vasilina Zayats, Milan Melicherik, Jannette Carey, Rüdiger Ettrich [Academy of Sciences of the Czech Republic]

See Applications / Ligand Binding.

- 2329 **Biomimetic polymers of plant cutin: an approach from molecular modeling** ,Miguel A. San-Miguel [Universidad de Sevilla], Jaime Oviedo, Jose Alejandro Heredia-Guerrero, Antonio Heredia, Jose Jesus Benitez

Biomimetics of materials is based on adopting and reproducing a model in *nature* with a well-defined functionality optimized through evolution. An example is barrier polymers that protect living tissues from the environment. In this work, we present a combined study using experimental and simulation techniques on self-assembled layers of monomers selectively functionalized with hydroxyl groups.

- 2328 **Theoretical studies of separation of *cis-trans* isomers using dinuclear (Cu^{2+} - and Zn^{2+} -based) cryptates** ,Sateesh Bandaru [University College Dublin], Niall J. English, J. M. D. MacElroy

Theoretical investigations have been carried out using density functional theory, with the M06L functional and SMD solvent-modeling, to study the binding interactions of geometrical *cis-trans* isomers of fumarate (fum^{2-}), maleate (male^{2-}) and 1,2-cyclopropane dicarboxylate with Cu^{2+} - and Zn^{2+} -based dinuclear cryptates.

- 2326 Theoretical study of solvent effects on RDX crystal quality and sensitivity using an implicit solvation model , Gang Chen, Wenyan Shi, Mingzhu Xia [Nanjing University of Science and Technology], Wu Lei, Fengyun Wang, Xuedong Gong

Density functional theory calculations using an SMD model were performed to investigate the effect of solvents (cyclohexanone, acetone, dimethyl formamide and dimethyl sulphoxide) on the crystal quality and sensitivity of RDX.

- 2325 **Role of sulfonation in the stability, reactivity, and selectivity of poly(ether imide) used to develop ion exchange membranes: DFT study with application to fuel cells** , Ernesto López-Chávez [Colegio de Ciencia y Tecnología de la Universidad Autónoma de la Ciudad de México], Yésica A. Peña-Castañeda, L. César de la Portilla-Maldonado, Javier Guzmán-Pantoja, José Manuel Martínez-Magadán, Raúl Oviedo-Roa, Fray de Landa Castillo-Alvarado, Armando Cruz-Torres

A study utilizing density functional theory (DFT) to elucidate the effect of the degree of sulfonation on the chemical stability, reactivity, and selectivity of poly(ether imide) (PEI), which allows the ionic transport properties of the membrane to be predicted, is reported here.

- 2324 **Exploring the structural and functional impact of the ALK F1174L mutation using bioinformatics approach** , Anish Kumar, K. Ramanathan [VIT University]

Crizotinib is the most effective and the only drug that has been approved for the treatment of anaplastic lymphoma kinase (ALK)-positive lung cancer. In this study, we used molecular docking and molecular dynamics (MD) approach to decipher the effect of F1174L mutation in drug–target binding.

- 2323 **Structural, electronic, and magnetic properties of the Fe-doped GaP nanotubes** ,Farideh Hajiheidari, Hamed Abbasian, Mahnaz Mohammadi[University of Kashan]

In this work we aimed to study the structural, electronic, and magnetic properties of the Fe-doped GaP nanotubes (GaPNTs).

- 2322 **Industrial applications of in silico ADMET , Bernd Beck** [Boehringer Ingelheim Pharma], **Tim Geppert**

Quantitative structure activity relationship (QSAR) modeling has been in use for several decades now. In this paper we describe some of the available methods and best practice for the different stages of the in silico model building process. We also describe some more recent developments, like automated model building and the prediction probability.

- 2321 **Testing the sensitivities of noncognate inhibitors to varicella zoster virus thymidine kinase: implications for postherpetic neuralgia therapy with existing agents , Lianjuan Yang, Xiaohui Mo, Hong Yang, Hejun Dai, Fei Tan** [The Fungal Reference Laboratory of Shanghai Dermatology Hospital]

In the present study, we attempted to test the sensitivities of HSV-1 TK inhibitors to their noncognate VZV TK by integrating in silico modeling and an in vitro assay. We tested nine representative HSV-1 TK inhibitors, including three FDA-approved drugs and six compounds that are under clinical development. The structures of the complexes of these inhibitor ligands with HSV-1 TK and noncognate VZV TK had been solved previously by X-ray crystallography or were modeled in the present work using a template-based approach.

- 2320 **Computational study of interactions and nuclear magnetic shielding constants in linear chains of formamide clusters ,Marina Sánchez, Rita Prosimi** [Instituto de Física Fundamental, IFF-CSIC], **Gerardo Delgado-Barrio**

We investigated the energetic, structural, dielectric, and nuclear magnetic shielding properties of linear n -formamide clusters, with n up to 6, to quantitatively characterize cooperative effects in model biological systems.

- 2319 **Elucidating the structural basis of diphenyl ether derivatives as highly potent enoyl-ACP reductase inhibitors through molecular dynamics simulations and 3D-QSAR study ,Pharit Kamsri, Auradee Punkvang, Patchareenart Saparpakorn, Supa Hannongbua, Stephan Irle, Pornpan Pungpo**[Ubon Ratchathani University]

See Applications / QSAR.

- 2318 **Indigo adsorption on a silicate surface: a theoretical density functional study ,Cristina Iuga** [Universidad Autónoma Metropolitana-Xochimilco], **C. Ignacio Sainz-Díaz, Elba Ortíz, Annik Vivier-Bunge**

In this work, we performed a quantum-mechanical theoretical study of the adsorption of the indigo molecule onto the (001) surface of a phyllosilicate. Different methods and approaches were applied and compared.

- 2317 **Potential energy function information from quantum phase shift using the variable phase method ,Nelson H. T. Lemes, João P. Braga** [Universidade Federal de Minas Gerais], **Márcio O. Alves, Éderson D'M. Costa**

The present work discusses quantum phase shift sensitivity analysis with respect to the potential energy function. A set of differential equations for the functional derivative of the quantum phase shift with respect to the potential energy function was established and coupled with the variable phase equation.

- 2316 **Computational chemistry of natural products: a comparison of the chemical reactivity of isonaringin calculated with the M06 family of density functionals**, Daniel Glossman-Mitnik[Complejo Industrial Chihuahua]

The M06 family of density functionals has been assessed for the calculation of the molecular structure and properties of the Isonaringin flavonoid that can be an interesting material for dye-sensitized solar cells (DSSC).

- 2315 **A detailed reactive cross section study of $X + Li_2 \rightarrow Li + LiX$, with $X = H, D, T$, and Mu** , Wiliam F. da Cunha, Luciano A. Leal, Thiago F. da Cunha, Geraldo M. e Silva, João B. L. Martins, Ricardo Gargano[University of Brasília]

In this work we apply quasiclassical trajectory theory to the $X + Li_2 \rightarrow Li + LiX$ reactions, with X standing for H, D, T, and Mu, in order to determine dynamical properties such as state-to-state reactive cross-section, rotational, vibrational, and translational product distributions.

- 2314 **Evaluation of active designs of cephalosporin C acylase by molecular dynamics simulation and molecular docking**, Qing Li, Xiaoqiang Huang, Yushan Zhu [Tsinghua University]

See Applications / Enzyme Catalysis.

- 2309 **Theoretical studies on organic D- π -A sensitizers with planar triphenylamine donor and different π -linkers for dyes-sensitized solar cells**, Hai-Bin Li, Jian-Zhao Zhang, Ji Zhang, Yong Wu, Yi-Ai Duan, Zhong-Min Su, Yun Geng [Northeast Normal University]

Systematic density functional theory (DFT) and time-dependent DFT calculations on the geometry, electronic structure, absorption, and nonlinear optical (NLO) properties of experimentally synthesized organic sensitizers **LCn** ($n = 1-3$) used in dyes-sensitized solar cells (DSSCs) were performed to disclose the important influences of the planar triphenylamine donor and the extended π -linker on the DSSCs performance.

- 2299 **Structural and electronic study of neutral, positive, and negative small rhodium clusters $[Rh_n, Rh_n^+, Rh_n^-; n = 10-13]$** , M. A. Mora [Universidad Autónoma Metropolitana], M. A. Mora-Ramirez

We have carried out a systematic study for the determination of the structure and the fundamental state of neutral and ionic small rhodium clusters $[Rh_n, Rh_n^+, Rh_n^-; n = 10-13]$ using ab initio Hartree-Fock methods with a LANL2DZ basis set. A range of spin multiplicities is investigated for each cluster.

- 2298 **Rovibrational energy and spectroscopic constant calculations of $CH_4 \cdots CH_4$, $CH_4 \cdots H_2O$, $CH_4 \cdots CHF_3$, and $H_2O \cdots CHF_3$ dimers**, Wiliam F. Cunha, Ricardo Gargano, Edgardo Garcia, José R. S. Politi, Alessandra F. Albernaz, João B. L. Martins[University of Brasilia]

In this work, we performed a thorough investigation of potential energy curves, rovibrational spectra, and spectroscopic constants for dimers whose interactions are mediated by hydrogen bonds and other hydrogen interactions.

- 2297 **Alternative analytical forms to model diatomic systems based on the deformed exponential function**, José Erinaldo da Fonseca, Heibbe Cristhian B. de Oliveira, Wiliam Ferreira da Cunha, Ricardo Gargano[University of Brasília]

Using a deformed exponential function and the molecular-orbital theory for the simplest molecular ion, two new analytical functions are proposed to represent the potential energy of ground-state diatomic systems.

- 2296 **Thermodynamic and conformational insights into the phase transition of a single flexible homopolymer chain using replica exchange Monte Carlo method**, Lei Wang [University of Science and Technology of China], Ningning Li, Shiyan Xiao, Haojun Liang

The phase transition of a single flexible homopolymer chain in the limit condition of dilute solution is systematically investigated using a coarse-grained model. Replica exchange Monte Carlo method is used to enhance the performance of the conformation space exploration, and thus detailed investigation of phase behavior of the system can be provided.

- 2295 **DFT study of sulfur derivatives of cumulenes and their protonated forms of interstellar interest and calculations of dissociation energies of protonated forms $(\text{SC}(\text{CH})\text{C}_n\text{-2S})^+$ ($n=3-8$)**, Mohamed Ali Benmensour, Sema Djennane-Bousmaha [Laboratoire de Thermodynamique et Modélisation Moléculaire], Abdou Boucekkine

A theoretical study of the sulfur cumulenes SC_nS ($n=3-8$), C_nS ($n=1-8$) and of their protonated forms $(\text{SC}_n\text{S})\text{H}^+$ and $(\text{C}_n\text{S})\text{H}^+$ that might exist in the interstellar environment, has been carried out by means of the standard B3LYP/6-311G** method.

- 2289 **Improved hybrid optimization algorithm for 3D protein structure prediction**, Changjun Zhou [Dalian University], Caixia Hou, Xiaopeng Wei, Qiang Zhang

A new improved hybrid optimization algorithm - PGATS algorithm, which is based on toy off-lattice model, is presented for dealing with three-dimensional protein structure prediction problems.

- 2288 **Theoretical study on the reaction mechanism of carbaryl with OH radicals**, Shengmin Sun, Kun Zhang, Yang Lu, Aihua Wang, Hui Zhang [Harbin University of Science and Technology]

A theoretical investigation on the multiple-channel degradation mechanism of carbaryl with $\cdot\text{OH}$ in the atmosphere was completed by the variational transition state theory. Eleven reaction channels have been identified using the density functional theory.

- 2285 **The low-lying electronic states of ReB**, Antonio Carlos Borin [Universidade de São Paulo], João Paulo Gobbo, César Augusto Milani Castro

The ground and low-lying electronic states of ReB were studied at the CASPT2//CASSCF level (multiconfigurational second-order perturbation theory) and quadruple- ζ ANO-RCC basis sets.

- 2284 **Partly saturated polyacene structures: a theoretical study**, Muammar El Khatib, Stefano Evangelisti [Université de Toulouse (UPS) et CNRS (UMR-5626)], Thierry Leininger, Gian Luigi Bendazzoli

Planar molecular edifices obtained by joining polyacene fragments (polyacene stripes) are investigated at tight-binding (i.e., with a Hückel Hamiltonian) and ab initio level.

- 2280 **Theoretical studies on degradation mechanism for OH-initiated reactions with diuron in water system**, Xiaohua Ren [Weifang University of Science and Technology], Zhaojie Cui, Youmin Sun

In this work, the degradation mechanisms for OH-induced reactions of diuron in water phase are investigated at the MPWB1K/6-311+G(3df,2p)//MPWB1K/6-31+G(d,p) level with polarizable continuum model (PCM) calculation.

- 2276 **Apparent basicities of the surfaces characterizing the dominant crystal habits of distinct polymorphic forms of 4-aminosulfonamide**, Piotr Cysewski [Nicolaus Copernicus University in Toruń,]

A new approach for estimating local basicities/aciditys of groups exposed on crystal surfaces was formulated and validated. The model, constructed within a quantitative structure–property relationship (QSPR) framework, allowed the expression of the protonic properties of amine and sulfonamide groups as functions of simple molecular descriptors of geometric types.

- 2275 **Substituent effects on molecular properties of dicarba-closo-dodecarborane derivatives**, Georgia M. A. Junqueira [Universidade Federal de Juiz de Fora], Fernando Sato

In this paper we study the role played by substituent effects on reactivity and NLO properties of *ortho*-, *meta*- and *para*- dicarba-closo-dodecarborane derivatives at B3LYP/6-31G(d,p) level of theory.

- 2260 **Computational study of graphene growth on copper by first-principles and kinetic Monte Carlo calculations**, Simone Taioli [FBK-Center for Materials and Microsystems and University of Trento]

In this work the growth of a graphene monolayer on copper substrate, as typically achieved via chemical vapor deposition of propene (C₃H₆), was investigated by first-principles and kinetic Monte Carlo calculations.

- 2256 **Spherical tensor multipolar electrostatics and smooth particle mesh Ewald summation: a theoretical study**, François Zielinski, Paul L. A. Popelier [University of Manchester]

The point-charge approximation, typically used by classical molecular mechanics force-fields, can be overcome by a multipolar expansion. For decades multipole moments were only used in the context of the rigid body approximation but recently it has become possible to combine multipolar electrostatics with molecular flexibility.

- 2251 **A comparison of various optimization algorithms of protein–ligand docking programs by fitness accuracy**, Liyong Guo, Zhiqiang Yan, Xiliang Zheng, Liang Hu, Yongliang Yang, Jin Wang [Chinese Academy of Sciences]

See Applications / Membrane protein and Lipid- peptide Interactions.

- 2248 **Modeling bacterial quorum sensing in open and closed environments: potential discrepancies between agar plate and culture flask experiments**, Dóra Bihary, Marietta Tóth, Ádám Kerényi, Vittorio Venturi, Sándor Pongor [Pázmány Péter Catholic University]

Quorum sensing (QS) is a process of bacterial communication and cooperation mediated by the release of jointly exploited signals and “public goods” into the environment. Namely, mutants that appear perfectly viable and capable of outgrowing wild type cells in a closed model system such as a culture flask, may not be

viable or invasive on open surfaces such as agar plates. Here we show via agent-based computational simulations that this apparent discrepancy is due to the difference between open and closed systems.

- 2240 **A rational reduction of CI expansions: combining localized molecular orbitals and selected charge excitations** , Tim Krah [Université de Strasbourg], Nadia Ben Amor, Daniel Maynau, J. A. Berger, Vincent Robert

Based on localized molecular orbitals, the proposed method reduces large configuration interaction (CI) spaces while maintaining agreement with reference values. Our strategy concentrates the numerical effort on physically pertinent CI-contributions and is to be considered as a tool to tackle large systems including numerous open-shells.

- 2237 **Complexity measure and quantum shape-phase transitions in the two-dimensional limit of the vibron model** , Elvira Romera [Universidad de Granada], Manuel Calixto, Ágnes Nagy

We obtain a characterization of quantum shape-phase transitions in the terms of complexity measures in the two-dimensional limit of the vibron model based on the spectrum generating algebra $U(3)$. Complexity measures (in terms of the Rényi entropies) have been calculated for different values of the control parameter for the ground state of this model giving sharp signatures of the quantum shape-phase transition from linear to bent molecules.

- 2231 **Understanding electrostatic and steric requirements related to hypertensive action of AT₁ antagonists using molecular modeling techniques** , Danielle da C. Silva, Vinicius G. Maltarollo, Emmanuela Ferreira de Lima, Karen Cacilda Weber, Kathia M. Honorio [Universidade Federal do ABC]

See Applications / Ligand Binding.

- 2226 **An innovative synergistic grid approach to the computational study of protein aggregation mechanisms** , Noelia Faginas-Lago [University of Perugia], Margarita Albertí, Alessandro Costantini, Antonio Laganà, Andrea Lombardi, Leonardo Pacifici

See Applications / Protein Dynamics.

- 2225 **Natural bond orbital/natural J-coupling study of vicinal couplings** , José M. García de la Vega, Jesús San Fabián [Universidad Autónoma de Madrid]

NBO-NJC decomposition of vicinal $^3J_{HH}$ spin-spin coupling constants into Lewis, delocalization, and repolarization contributions are presented. A deep study allows to assign the main contributions to specific orbitals or electron delocalizations between two orbitals.

Journal of Molecular Modeling, 20 (8), July, 2014.

- 2399 **Dual-inhibitors of STAT5 and STAT3: studies from molecular docking and molecular dynamics simulations**, Shengjuan Shao, Rilei Yu, Yanqing Yu, Yanni Li [Tianjin University]

See Applications / Medicinal Chemistry and Drug Design.

- 2398 **Developing polarizable potential for molecular dynamics of Cm(III)-carbonate complexes in liquid water**, Riccardo Spezia [Université d'Evry Val d'Essonne], Yannick Jeanvoine, Rodolphe Vuilleumier

In this work we have developed a polarizable potential to study Cm(III) forming complexes with carbonate anions in liquid water. The potential was developed by employing an extension of the procedure that we used to study the hydration of lanthanoids(III) and actinoids(III). Force field performances were benchmarked against DFT results obtained by both geometry optimization and Car-Parrinello molecular dynamics.

- 2395 **External electric field effects on the mechanical properties of the $\alpha\beta$ -tubulin dimer of microtubules: a molecular dynamics study**, H. R. Saeidi, A. Lohrasebi [University of Isfahan], K. Mahnam

See Applications / Protein Dynamics.

- 2394 **Sodium binding to hH₃R and hH₄R — a molecular modeling study**, Hans-Joachim Wittmann, Roland Seifert, Andrea Strasser [University of Regensburg]

See Methodology / Molecular Dynamics.

- 2391 **Silver- and gold-mediated nucleobase bonding**, Paulo H. Acioli [Northeastern Illinois University], Sudha Srinivas

We report the results of a density functional theory investigation of the bonding of nucleobases mediated by silver and gold atoms in the gas phase.

- 2390 **Understanding the thermal [1s,5s] hydrogen shift isomerization of ocimene**, Eduardo Chamorro [Universidad Andres Bello], Pablo Ruiz, Jairo Quijano, Diana Luna, Laura Restrepo, Sandra Zuluaga, Mario Duque-Noreña

α -Ocimene, β -ocimenes and alloocimenes are isomeric monoterpenes occurring naturally as oils within several plants and fruits. In this work, and in the context of a recent revival in attention on the subject, we provide new theoretical insights concerning the nature of the electronic reorganization driving the decomposition of cis- β -ocimene to alloocimene.

- 2389 **De novo tertiary structure prediction using RNA123—benchmarking and application to Macugen**, Emma S. E. Eriksson [University of Gothenburg], Lokesh Joshi, Martin Billeter, Leif A. Eriksson

The RNA123 program was applied to predict the tertiary structure of the RNA segment of Macugen®, the first RNA aptamer approved for clinical use, and for which no tertiary structure has yet been solved. Four possible tertiary structures were predicted for this 27-nucleic-acid-long RNA molecule, which will be used in constructing a full model of the PEGylated aptamer and its interaction with the vascular endothelial growth factor target.

- 2388 **Theoretical study of the NLO responses of some natural and unnatural amino acids used as probe molecules**, S. N. Derrar, M. Sekkal-Rahal [Université Djilali Liabès], P. Derreumaux, M. Springborg

The first hyperpolarizabilities β of the natural aromatic amino acids tryptophan and tyrosine have been investigated using several methods and basis sets. Some of the theoretical results obtained were compared to the only experimental hyper-Rayleigh scattering data available.

- 2386 **Methyl-methoxypyrrolinone and flavinium nucleus binding signatures on falcipain-2 active site**, Olaposi I. Omotuyi [Nagasaki University]

Following the increasing reports of human toxicity and plasmodium resistance to artemisinin and its derivatives, falcipain-2 (FP-2) is now emerging as the choice antimalarial drug target. The structural bases for their inhibitory actions have been studied using molecular dynamics simulation. Myricetin and fisetin act as proton transfer tunnel breakers by inserting between His174 and Cys42, which are key active site residues of FP-2, stenopalustroside inhibits the polarization of His174 by Asn173; a major preparatory step for Cys42/His174 proton transfer process.

- 2385 **Probing the structural and electronic properties of bimetallic chromium-gold clusters $\text{Cr}_m\text{Au}_n (m + n \leq 6)$: comparison with pure chromium and gold clusters**, Peng Lu [Tianjin Polytechnic University], Guang-Hua Liu, Xiao-Yu Kuang

Bimetallic chromium-gold $\text{Cr}_m\text{Au}_n (m + n \leq 6)$ clusters are systematically investigated using the density functional theory at PW91P86 level with LanL2TZ basis set to understand the evolution of various structural, electronic, magnetic, and energetic properties as a function of size $(m + n)$ and composition (m/n) of the system.

- 2384 **Spectroscopic and quantum mechanical investigation of N,N' -bisarylmalonamides: solvent and structural effect**, Violeta M. Arsović, Bojan Đ. Božić, Jelena M. Mirković, Vesna D. Vitnik, Željko J. Vitnik, Walter M. F. Fabian, Slobodan D. Petrović, Dušan Ž. Mijin [University of Belgrade]

The UV absorption spectra of ten N,N' -bisarylmalonamides have been recorded in the range 200–400 nm in a set of selected solvents. The solute–solvent interactions have been analyzed on the basis of the linear solvation energy relationship (LSER) concept proposed by Kamlet and Taft.

- 2382 **Multi-reference Hartree-Fock configuration interaction calculations of LiH and Be using a new double-zeta atomic base**, Antonio Moreira de Cerqueira Sobrinho, Micael Dias de Andrade, Marco Antônio Chaer Nascimento, Luiz Augusto Carvalho Malbouisson [Instituto de Física da UFBA]

In this work, we propose new double-zeta atomic bases for the Li and Be atoms. These were obtained by applying the Hartree-Fock-Gauss generalized simulated annealing (GSA) method—a modified form of the GSA algorithm.

- 2381 **Unzipping of neuronal snare protein with steered molecular dynamics occurs in three steps** , Mustafa Tekpinar [Yuzuncu Yil University], Wenjun Zheng

Soluble NSF-attachment protein receptors (SNAREs) play a crucial role in membrane fusion. Neuronal SNAREs, a four-helix bundle, help synaptic vesicles fuse with plasma membranes. We applied constant velocity pulling forces in silico to C terminal of synaptobrevin, one of the helices in the bundle, to understand unzipping mechanism of neuronal SNAREs.

- 2380 **Insight into HIV-1 reverse transcriptase–aptamer interaction from molecular dynamics simulations** ,Niran Aeksiri, Napat Songtawee, M. Paul Gleeson, Supa Hannongbua, Kiattawee Choowongkomon[Kasetsart University]

See Applications / Protein Confirmation Analysis.

- 2379 **Structure, aromaticity, stability, and energetic performance of the analogues and derivatives of s-heptazine** , Junqing Yang, Xuedong Gong[Nanjing University of Science and Technology], Guixiang Wang

s-heptazine is one of the most attractive polycyclic C-N precursors for graphitic carbon nitride materials (CNx). In this paper in order to find the relationships between the structure, aromaticity, and stability for this novel compound, its analogues with three conjoint six-membered rings (I ~ V) and derivatives with different substituents (VI-1 ~ VI-5) were investigated using the density functional theory method.

- 2378 **Comparison of several protocols for the computational prediction of the maximum absorption wavelength of chrysanthemin** , Rody Soto-Rojo, Jesús Baldenebro-López, Norma Flores-Holguín, Daniel Glossman-Mitnik[NANOCOSMOS Virtual Lab]

UV-Vis spectra were calculated using time-dependent density functional theory for the chrysanthemin pigment, which is used as natural dye in dye sensitized solar cells. To this end, we studied four different calculation protocols in order to obtain the best approximation according to the maximum absorption wavelength (λ_{max}) of the experimental spectrum.

- 2377 **Multiscale simulations of the structure and dynamics of stereoregular poly(methyl methacrylate)s** ,Chaofu Wu[Hunan University of Humanities Science & Technology]

The chain tacticity of a polymer is a key influence on its structure and dynamics, which ultimately determine its properties. In this work, two typical stereoregular poly(methyl methacrylate) melts were investigated via multiscale simulations. To improve computational efficiency, systematic coarse-graining was first performed.

- 2376 **Role of pH in structural changes for Pin1 protein: an insight from molecular dynamics study** ,Yu Wang, Lei Xi, Jie Yao, Jiao Yang, Lin-Fang Du[Sichuan University]

See Applications / Protein Dynamics.

- 2375 **Europium doped zinc sulfide: a correlation between experimental and theoretical calculations** ,Mateus M. Ferrer, Yuri V. B. de Santana, Cristiane W. Raubach, Felipe A. La Porta, Amanda F. Gouveia, Elson Longo, Julio R. Sambrano[São Paulo State University]

This paper presents the correlation among electronic and optical property effects induced by the addition of different concentrations of europium (Eu^{3+}) in zinc sulfide (ZnS) by microwave-assisted solvothermal (MAS) method.

- 2374 **Main chemical species and molecular structure of deep eutectic solvent studied by experiments with DFT calculation: a case of choline chloride and magnesium chloride hexahydrate** ,Chao Zhang [Chinese Academy of Sciences], Yongzhong Jia, Yan Jing, Huaiyou Wang, Kai Hong

The infrared spectrum of deep eutectic solvent of choline chloride and magnesium chloride hexahydrate was measured by the FTIR spectroscopy and analyzed with the aid of DFT calculations.

- 2373 **Theoretical study of adsorption of nitrogen-containing environmental contaminants on kaolinite surfaces** ,Andrea Michalkova Scott [US Army Engineer Research and Development Center (ERDC)], Elizabeth A. Burns, Frances C. Hill

The adsorption of nitrogen-containing compounds (NCCs) including 2,4,6-trinitrotoluene (TNT), 2,4-dinitrotoluene (DNT), 2,4-dinitroanisole (DNAN), and 3-nitro-1,2,4-triazol-5-one (NTO) on kaolinite surfaces was investigated.

- 2372 **The CH_3PH_2 and CH_3PH isomers: isomerization, hydrogen release, thermodynamic, and spectroscopy properties** ,Rommel B. Viana[Universidade de São Paulo], Albérico B. F. da Silva

In this study was performed a quantum chemical investigation of the methylphosphine molecule and its radical, which may show potential implications in interstellar processes, and may be crucial atmospheric tracer gasses in the atmosphere of Giant planets.

- 2371 **Tunable electronic properties of ultra-thin boron-carbon-nitrogen heteronanotubes for various compositions** ,Yue Wang, Gang Huang, Juan Zhang, Qingyi Shao South China Normal University]

A first-principles calculation was carried out to investigate the stability and electronic properties of ultra-thin $\text{C}_x(\text{BN})_y$ heteronanotubes which were composed by joining pure CNT and BNNT segments with different composition and configurations.

- 2370 **Molecular dynamics studies on the influences of a gradient electric field on the water chain in a peptide nanotube** ,Hui Li, Jianfen F. Fan [Soochow University,], Rui Li, Yi Yu, Xiliang L. Yan

See Applications / Protein Dynamics.

- 2369 **A study of the interaction between HIV-1 protease and C_2 -symmetric inhibitors by computational methods** ,Shuhua Shi, Guodong Hu [Dezhou University], Xiumei Zhang, Jihua Wang

See Applications / Ligand Binding.

- 2368 **Topological analyses of time-dependent electronic structures: application to electron-transfers in methionine enkephalin** , Julien Pilmé [UPMC Université Paris], Eleonora Luppi, Jacqueline Bergès, Chantal Houée-Lévin, Aurélien de la Lande

We have studied electron transfers (ET) between electron donors and acceptors, taking as illustrative example the case of ET in methionine enkephalin. Recent pulse and gamma radiolysis experiments suggested that an ultrafast ET takes place from the C-terminal tyrosine residue to the N-terminal, oxidized, methionine residue.

- 2366 **Conformational space and vibrational spectra of 2-[(2,4-dimethoxyphenyl)amino]-1,3-thiazolidin-4-one** , Alicja Nowaczyk [Nicolaus Copernicus University], Marcin Kowiel, Andrzej Gzella, Łukasz Fijałkowski, Volodymyr Horishny, Roman Lesyk

In this work we present the results of a study of the X-ray structure of 2-[(2,4-dimethoxyphenyl)amino]-1,3-thiazolidin-4-one.

- 2365 **Study of interaction of human serum albumin with curcumin by NMR and docking** , Durg Vijay Singh, Santosh Kumar Bharti, Shikha Agarwal, Raja Roy, Krishna Misra [Centre of Biomedical Research, Raebareli Road]

Curcumin has been reported to be therapeutically active but has poor bioavailability, half life, and high rate of metabolic detoxification. The present study is focused to analyze interaction of curcumin with HSA by NMR and docking studies. In order to investigate the binding affinity of curcumin with HSA, NMR based diffusion techniques and docking study have been carried out.

- 2364 **Examine the characterization of biofilm formation and inhibition by targeting SrtA mechanism in Bacillus subtilis: a combined experimental and theoretical study** , Chandrabose Selvaraj, Jeyachandran Sivakamavalli, Baskaralingam Vaseeharan, Poonam Singh, Sanjeev Kumar Singh [Alagappa University]

Bacillus subtilis is one of the well-known biofilm-forming organisms associated with plants, animals, and also used as a model organism for all Bacillus sp. . Here in this study we concluded the computationally screened SrtA inhibitors showed high level of biofilm inhibition despite difficulties in bacterial membrane rigidification.

- 2363 **Hydrogen bond coupling in sodium dihydrogen triacetate** , Ashour A. Ahmed, Rifaat H. Hilal, Mohamed F. Shibl [Cairo University]

The coupling of hydrogen bonds is central to structures and functions of biological systems. Hydrogen bond coupling in sodium dihydrogen triacetate (SDHTA) is investigated as a model for the hydrogen bonded systems of the type O-H...O.

- 2362 **Is 1-nitro-1-triazene a high energy density material?** , Weijie Chi, Ting Yan, Butong Li [Guizhou Normal College]

An azo bridge ($-N=N-$) can not only desensitize explosives but also dramatically increase their heats of formation and explosive properties. Amino and nitro are two important high energy density functional groups. Here, we present calculations on 1-nitro-1-triazene ($NH_2-N=N-NO_2$).

- 2361 **Insight into the informational-structure behavior of the Diels-Alder reaction of cyclopentadiene and maleic anhydride** , Moyocoyani Molina-Espíritu [Universidad Autónoma Metropolitana-Iztapalapa], Rodolfo

O. Esquivel, Miroslav Kohout, Juan Carlos Angulo, José A. Dobado, Jesús S. Dehesa, Sheila LópezRosa, Catalina Soriano-Correa

The course of the Diels-Alder reactions of cyclopentadiene and maleic anhydride were studied. Two reaction paths were modelled: endo- and exo-selective paths. All structures within the transient region were characterized and analyzed by means of geometrical descriptors, physicochemical parameters and information-theoretical measures in order to observe the linkage between chemical behavior and the carriage of information.

- 2360 **Phonon density of states from the experimental heat capacity: an improved distribution function for solid aluminium using an inverse framework** , Éderson D'M. Costa, Nelson H. T. Lemes [Universidade Federal de Alfenas], Márcio O. Alves, João P. Braga

In this study it is reported the retrieval of the phonon density of states for solid aluminium from the temperature dependent heat capacity, the inverse heat capacity problem.

- 2359 **Establishing conditions for simulating hydrophobic solutes in electric fields by molecular dynamics** ,Zoran Miličević, Siewert J. Marrink, Ana-Sunčana Smith, David M. Smith[Friedrich-Alexander University Erlangen-Nuremberg]

Despite considerable effort over the last decade, the interactions between solutes and solvents in the presence of electric fields have not yet been fully understood. A very useful manner in which to study these systems is through the application of molecular dynamics (MD) simulations. We explain the spread in observed mobilities by performing extensive molecular dynamics simulations using the GROMACS software package on a system consisting of a model hydrophobic object (Lennard-Jones particle) immersed in water both in the presence and absence of a static electric field.

- 2357 **Evidence supporting the existence of a NUPR1-like family of helix-loop-helix chromatin proteins related to, yet distinct from, AT hook-containing HMG proteins** ,Raul Urrutia[Center for Individualized Medicine., Mayo Clinic], Gabriel Velez, Marisa Lin, Gwen Lomberg, Jose Luis Neira, Juan Iovanna

NUPR1, a small chromatin protein, plays a critical role in cancer development, progression, and resistance to therapy. Here, using a combination of structural bioinformatics and molecular modeling methods, we report several novel findings that enhance our understanding of the biochemical function of this protein.

- 2356 **Substituent effects in hydrogen bonding: DFT and QTAIM studies on acids and carboxylates complexes with formamide** , Borys Ośmiałowski[University of Technology and Life Sciences, Seminaryjna 3]

Four series of hydrogen bonded complexes of formamide and substituted benzoic acids and benzoates were studied in the light of substituent effect on intermolecular interactions.

- 2355 **Spin-orbit splitting for inner-shell 2p states** , Alexandre B. Rocha[Universidade Federal do Rio de Janeiro]

A strategy to calculate spin-orbit splitting for inner-shell transitions at an ab initio level is presented. The initial wave function is calculated for a spinless Hamiltonian at a multiconfigurational level, with just a few configurations, followed by multireference configuration interaction in order to establish a set of singlet and triplet states at 2p excitation edge.

- 2354 **Theoretical approach to the innovative mutation of naphthalene 1,2-dioxygenase: a molecular dynamics and docking study** , Vito Librando [Università di Catania], Matteo Pappalardo

Polycyclic aromatic hydrocarbons are a family of ubiquitous pollutants whose environmental behavior has been widely studied. One of the best-studied enzymes is naphthalene 1,2-dioxygenase (NDO). Herein, we describe the study of NDO using molecular dynamics and docking calculations to discover new mutants with high degrading capabilities.

- 2352 **Substituent effects in 1-nitro-4-substituted bicyclo[2.2.2]octane derivatives: inductive or field effects?** ,Tadeusz M. Krygowski, Wojciech P. Oziminski[University of Warsaw]

Interactions between the NO₂ group and 13 different substituents (BF₂, BH₂, CF₃, CH₃, CHO, CN, F, NH₂, NMe₂, NO, OH, OMe) were investigated computationally for bicyclo[2.2.2]octane (BCO) and benzene substituted at 1,4 and 1,3 positions in the ring.

- 2351 **Driving and retarding forces in a chemical reaction** , Peter Politzer [University of New Orleans], Jane S. Murray, Diana Yepes, Pablo Jaque

The reaction force $F(\xi)$ is the negative gradient of the potential energy of a chemical process along the intrinsic reaction coordinate ξ . We extend the rigorous concept of $F(\xi)$ to the “activation strain model” of Bickelhaupt et al., to formulate the “strain” force $F_{\text{str}}(\xi)$ that retards a reaction and the “interaction” force $F_{\text{int}}(\xi)$ that drives it.

- 2342 **A theoretical study on diastereoselective oxidative dearomatization by iodoxybenzoic acid** ,Vincent Tognetti [Université de Rouen], Agathe Boulangé, Philippe A. Peixoto, Xavier Franck, Laurent Joubert

The reaction mechanism of diastereoselective oxidative dearomatization by iodoxybenzoic acid of key compounds involved in the total synthesis of epicocconone analogs, which are efficient fluorophores with a wide range of applications in protein staining and separation, was studied using density functional theory.

- 2338 **Structural insights into selective agonist actions of tamoxifen on human estrogen receptor alpha** ,Sandipan Chakraborty, Pradip Kumar Biswas[Tougaloo College]

Tamoxifen—an anti-estrogenic ligand in breast tissues used as a first-line treatment in estrogen receptor (ER)-positive breast cancers—is associated with the development of resistance followed by resumption of tumor growth in about 30 % of cases.

- 2327 **Theoretical studies on the stability, detonation performance and possibility of synthesis of the nitro derivatives of epoxyethane** ,Xueli Zhang, Xuedong Gong[Nanjing University of Science and Technology]

Compounds with heterocyclic rings and NO₂ groups have drawn much attention as high energy density compounds in recent years. In this study, the nitro derivatives 1–4 of epoxyethane (ETO) were investigated, and their synthetic possibilities in thermodynamics and thermal stability were predicted.

- 2306 **A unified coarse-grained model of biological macromolecules based on mean-field multipole–multipole interactions** ,Adam Liwo [University of Gdańsk, ul. Wita Stwosza 63], Maciej Baranowski, Cezary Czaplewski, Ewa Gołaś, Yi He, Dawid Jagieła, Paweł Krupa, Maciej Maciejczyk, Mariusz

Makowski, Magdalena A. Mozolewska, Andrei Niadzvedtski, Stanisław Oldziej, Harold A. Scheraga, Adam K. Sieradzan, Rafał Ślusarz, Tomasz Wirecki, Yanping Yin, Bartłomiej Zaborowski

A unified coarse-grained model of three major classes of biological molecules—proteins, nucleic acids, and polysaccharides—has been developed. It is based on the observations that the repeated units of biopolymers (peptide groups, nucleic acid bases, sugar rings) are highly polar and their charge distributions can be represented crudely as point multipoles.

Journal of Computational Chemistry, 35 (18), July, 2014.

- 1339–1346 **Performance of DFT+U method for prediction of structural and thermodynamic parameters of monazite-type ceramics** ,Ariadna Blanca Romero, Piotr M. Kowalski [Forschungszentrum Jülich], George Beridze, Hartmut Schlenz , Dirk Bosbach

We performed a density functional theory (DFT) study of the monazite-type ceramics using DFT+U method, where the Hubbard U parameters are derived ab initio, with the main goal in testing the predictive power of this computational method for modeling of f-electron materials that are of interest in nuclear waste management.

- 1347–1355 **Massively parallel implementation of 3D-RISM calculation with volumetric 3D-FFT** ,Yutaka Maruyama, Norio Yoshida[Kyushu University], Hiroto Tadano, Daisuke Takahashi, Mitsuhisa Sato ,Fumio Hirata

A new three-dimensional reference interaction site model (3D-RISM) program for massively parallel machines combined with the volumetric 3D fast Fourier transform (3D-FFT) was developed, and tested on the RIKEN K supercomputer.

- 1356–1363 **Cyclobutadiene automerization and rotation of ethylene: Energetics of the barriers by using Spin-polarized wave functions** ,Emilio San-Fabián [Universidad de Alicante] ,Federico Moscardó

Spin-projected spin polarized Møller–Plesset and spin polarized coupled clusters calculations have been made to estimate the cyclobutadiene automerization, the ethylene torsion barriers in their ground state, and the gap between the singlet and triplet states of ethylene.

- 1364–1370 **Site-directed analysis on protein hydrophobicity** ,Song-Ho Chong , Sihyun Ham[Sookmyung Women's University]

Hydrophobicity of a protein is considered to be one of the major intrinsic factors dictating the protein aggregation propensity. Here, we investigate how the hydrophobicity of constituent amino acid residues depends on the protein context.

- 1371–1387 **Pairwise decomposition of an MMGBSA energy function for computational protein design** ,Thomas Gaillard , Thomas Simonson[Laboratoire de Biochimie (CNRS UMR7654)]

See Applications / Protein Confirmation Analysis.

- 1388–1394 **^1H and ^{13}C NMR scaling factors for the calculation of chemical shifts in commonly used solvents using density functional theory** ,Gregory K. Pierens [The University of Queensland]

Calculation of NMR chemical shifts and coupling constants using quantum mechanical calculations [density functional theory (DFT)], has become a very popular tool for the determination of conformation and the assignment of stereochemistry within a molecule. We present the scaling factors (linear regression parameters) from 10 DFT methods for 10 commonly used NMR solvents using the same set of reference compounds.

- 1395–1409 **QuBiLS-MIDAS: A parallel free-software for molecular descriptors computation based on multilinear algebraic maps** ,César R. García-Jacas, Yovani Marrero-Ponce [Universidad Central “Martha Abreu” de Las Villas], Liesner Acevedo-Martínez, Stephen J. Barigye, José R. Valdés-Martín and Ernesto Contreras-Torres

The present report introduces the QuBiLS-MIDAS software belonging to the ToMoCoMD-CARDD suite for the calculation of three-dimensional molecular descriptors (MDs) based on the two-linear (bilinear), three-linear, and four-linear (multilinear or N-linear) algebraic forms. Thus, it is unique software that computes these tensor-based indices.

Journal of Computational Chemistry, 35 (19), July, 2014.

- 1411–1417 **Simulations of remote mutants of dihydrofolate reductase reveal the nature of a network of residues coupled to hydride transfer** ,Daniel Roston[University of Wisconsin], Amnon Kohen, Dvir Doron ,Dan T. Major

Recent experimental and theoretical studies have proposed that enzymes involve networks of coupled residues throughout the protein that participate in motions accompanying chemical barrier crossing. Here, we have examined portions of a proposed network in dihydrofolate reductase (DHFR) using quantum mechanics/molecular mechanics simulations.

- 1418–1429 **Modeling the electrostatic potential of asymmetric lipopolysaccharide membranes: The MEMPOT algorithm implemented in DelPhi** ,Roberta P. Dias, Lin Li, Thereza A. Soares , Emil Alexov [Clemson University]

Four chemotypes of the rough lipopolysaccharides (LPS) membrane from *Pseudomonas aeruginosa* were investigated by a combined approach of explicit water molecular dynamics (MD) simulations and Poisson–Boltzmann continuum electrostatics with the goal to deliver the distribution of the electrostatic potential across the membrane.

- 1430–1437 **Transformation between α -helix and β -sheet structures of one and two polyglutamine peptides in explicit water molecules by replica-exchange molecular dynamics simulations** ,Hsin-Lin Chiang, Chun-Jung Chen, Hisashi Okumura ,Chin-Kun Hu [Academia Sinica]

See Applications / Protein Secondary Structure.

- 1438–1445 **Efficient parameterization of torsional terms for force fields** ,Steven K. Burger, Paul W. Ayers[University of Toronto] , Jeremy Schofield

A novel method is presented for fitting force-field dihedral angles using an ensemble of structures generated from an ab initio Monte Carlo simulation. Importance sampling is used to achieve an efficient algorithm using

a low level of theory to minimize the system at each step with the dihedral angles constrained, followed by dihedral fitting using the single point energies at a higher level of theory.

- 1446–1456 **Reaction mechanism of Ru(II) piano-stool complexes: Umbrella sampling QM/MM MD study**
Zdeněk Futera, Jaroslav V. Burda [Charles University in Prague]

See Applications / Protein-Nucleic Acid Interaction.

- 1457–1463 **A Molecular modeling study of the changes of some steric properties of the precatalysts during the olefin metathesis reaction**, Frans T. I. Marx, Johan H. L. Jordaen [North-West University], Gerhard Lachmann, Hermanus C. M. Vosloo

See Applications / Ligand Binding.

- 1464–1471 **A comparison of low and high activity precatalysts: Do the calculated energy barriers during the self-metathesis reaction of 1-Octene correlate with the precatalyst metathesis activity?**, Frans T. I. Marx, Johan H. L. Jordaen [North-West University], Gerhard Lachmann, Hermanus C. M. Vosloo

The self-metathesis reaction of 1-octene with several well-known Grubbs-type precatalysts and the new Z-selective Grubbs precatalyst were studied with molecular modeling. The obtained Gibbs-free energy values for all the steps during the productive metathesis of 1-octene were compared to the values obtained for some low catalytic activity precatalysts.

Journal of Computational Chemistry, 35 (20), July, 2014.

- 1473–1480 **Acceleration of self-consistent field convergence in ab initio molecular dynamics simulation with multiconfigurational wave function**, Masaki Okoshi, Hiromi Nakai [Waseda University]

The Lagrange interpolation of molecular orbital (LIMO) method, which reduces the number of self-consistent field iterations in ab initio molecular dynamics simulations with the Hartree–Fock method and the Kohn–Sham density functional theories, is extended to the theory of multiconfigurational wave functions.

- 1481–1490 **Visualizing energy landscapes with metric disconnectivity graphs**, Lewis C. Smeeton, Mark T. Oakley, Roy L. Johnston [University of Birmingham]

The visualization of multidimensional energy landscapes is important, providing insight into the kinetics and thermodynamics of a system, as well the range of structures a system can adopt. In this study, we present a new software package, PyConnect, which is capable of producing both disconnectivity graphs and metric disconnectivity graphs in two or three dimensions.

- 1491–1498 **In silico concurrent multisite pH titration in proteins**, Hao Hu [University of Hong Kong], Lin Shen

See Applications / Protein Dynamics.

- 1499–1508 **Bay-type H···H “bonding” in cis-2-butene and related species: QTAIM versus NBO description**, Frank Weinhold [University of Wisconsin], Paul von Ragué Schleyer, William Chadwick McKee

We use comparative natural bond orbital (NBO) and quantum theory of atoms in molecules (QTAIM) methods to analyze the proximal bay-type $H\cdots H$ interactions in cis-2-butene and related species, which lead to controversial interpretation as attractive " $H-H$ bonding" in the QTAIM framework.

- 1509–1516 **Implementation of nuclear gradients of range-separated hybrid density functionals and benchmarking on rotational constants for organic molecules** ,Tobias Risthaus, Marc Steinmetz , Stefan Grimme[Universität Bonn]

We have implemented the nuclear gradient for several range-separated hybrid density functionals in the general quantum chemistry code ORCA. To benchmark the performance, we have used a recently published set of back-corrected gas phase rotational constants, which we extended by three molecules.

- 1517–1527 **Extension of accompanying coordinate expansion and recurrence relation method for general-contraction basis sets** ,Masao Hayami, Junji Seino , Hiromi Nakai [Waseda University]

An algorithm of the accompanying coordinate expansion and recurrence relation (ACE-RR), which is used for the rapid evaluation of the electron repulsion integral (ERI), has been extended to the general-contraction (GC) scheme.

- 1528–1531 **Gro2mat: A package to efficiently read gromacs output in MATLAB)** .Hung Dien, Charlotte M. Deane , Bernhard Knapp[Vienna University of Technology]

Molecular dynamics (MD) simulations are a state-of-the-art computational method used to investigate molecular interactions at atomic scale. Interaction processes out of experimental reach can be monitored using MD software, such as Gromacs.

Journal of Computational Chemistry, 35 (21), August, 2014.

- 1533–1544 **Interaction between ions and substituted buckybowls: A comprehensive computational study** ,Alba Campo-Cacharrón, Enrique M. Cabaleiro-Lago [Universidade de Santiago de Compostela] ,Jesús Rodríguez-Otero

Complexes formed by substituted buckybowls derived from corannulene and sumanene with sodium cation or chloride anion have been computationally studied by using a variety of methods. Best results have been obtained with the SCS-MP2 method extrapolated to basis set limit, which reproduces the highest-level values obtained with the MP2.X method.

- 1545–1551 **Drug release by pH-responsive molecular tweezers: Atomistic details from molecular modeling** ,Ahmed A. K. Mohammed, Steven K. Burger , Paul W. Ayers [McMaster University]

pH-responsive molecular tweezers have been proposed as an approach for targeting drug-delivery to tumors, which tend to have a lower pH than normal cells. We performed a computational study of a pH-responsive molecular tweezer using *ab initio* quantum chemistry in the gas-phase and molecular dynamics (MD) simulations in solution.

- 1552–1559 **Molecular dynamics with helical periodic boundary conditions** , Jiří Kessler , Petr Bouř
[Academy of Sciences, Prague]

Helical symmetry is often encountered in nature and thus also in molecular dynamics (MD) simulations. In many cases, an approximation based on infinite helical periodicity can save a significant amount of computer time. In the present study, we propose and investigate an algorithm comprising infinitely propagated helicity, which is compatible with commonly used MD software.

- 1560–1567 **The MC-DFT approach including the SCS-MP2 energies to the new minnesota-type functionals** , Po-Chun Liu , Wei-Ping Hu [National Chung Cheng University]

We have applied the multicoefficient density functional theory (MC-DFT) to four recent Minnesota functionals, including M06-2X, M08-HX, M11, and MN12-SX on the performance of thermochemical kinetics. The results indicated that the accuracy can be improved significantly using more than one basis set.

- 1568–1576 **On the mechanism of intramolecular nitrogen-atom hopping in the carbon chain of C₆N radical: A Plausible 3c–4e crossover π Long-Bond** , Gurpreet Kaur , Vikas [Panjab University]

Linear isomers of C₆N radical differ in the position of the nitrogen atom in the carbon chain of C₆N. Reaction routes, involving intramolecular nitrogen atom insertion at varying position in the carbon chain of C₆N, are analyzed for the isomerisation between linear isomers of C₆N.

- 1577–1591 **A supervised fitting approach to force field parametrization with application to the SIBFA polarizable force field** , Mike Devereux [University of Basel], Nohad Gresh, Jean-Philip Piquemal , Markus Meuwly

A supervised, semiautomated approach to force field parameter fitting is described and applied to the SIBFA polarizable force field. The I-NoLLS interactive, nonlinear least squares fitting program is used as an engine for parameter refinement while keeping parameter values within a physical range.

- 1592–1608 **Ermod: Fast and versatile computation software for solvation free energy with approximate theory of solutions** , Shun Sakuraba , Nobuyuki Matubayasi [Kyoto University]

ERmod is a software package to efficiently and approximately compute the solvation free energy using the method of energy representation. Molecular simulation is to be conducted at two condensed-phase systems of the solution of interest and the reference solvent with test-particle insertion of the solute.

Journal of Computational Chemistry, 35 (22), August, 2014.

- 1609–1617 **A two-scale approach to electron correlation in multiconfigurational perturbation theory** , Pooria Farahani, Daniel Roca-Sanjuán , Francesco Aquilante [Università di Bologna]

We present a new approach for the calculation of dynamic electron correlation effects in large molecular systems using multiconfigurational second-order perturbation theory (CASPT2).

- 1618–1620 **A graph-based short-cut to low-energy structures** ,Johannes M. Dieterich , Bernd Hartke
[Christian-Albrechts-University]

A new graph-based move class for global optimization of cluster structures is presented. Its performance and efficiency is analyzed for water clusters (H₂O)_n, n = 24, 61. This analysis indicates superior basin exploitation capabilities of the new move class for large clusters, compared to traditional moves.

- 1621–1629 **Implicit treatment of solvent dispersion forces in protein simulations** ,Sergio A. Hassan
[National Institutes of Health]

A model is proposed for the evaluation of dispersive forces in a continuum solvent representation for use in large-scale computer simulations. The model captures the short- and long-range effects of water-exclusion in conditions of partial and anisotropic hydration.

- 1630–1640 **Density functional theory study on mechanisms of epoxy-phenol curing reaction** ,My-Phuong Pham, Buu Q. Pham, Lam K. Huynh, Ha Q. Pham, Maurice J. Marks ,Thanh N. Truong[University of Utah]

A comprehensive picture on the mechanism of the epoxy-phenol curing reactions is presented using the density functional theory B3LYP/ 6-31G(d,p) and simplified physical molecular models to examine all possible reaction pathways.

- 1641–1645 **Evolution of chemical bonding and electron density rearrangements during D_{3h} → D_{3d} reaction in monolayered TiS₂: A QTAIM and ELF study** ,Maxim R. Ryzhikov, Vladimir A. Slepko, Svetlana G. Kozlova [Novosibirsk State University] , Svyatoslav P. Gabuda

Monolayered titanium disulfide TiS₂, a prospective nanoelectronic material, was previously shown to be subject to an exothermic solid-state D_{3h}–D_{3d} reaction that proceeds via a newly discovered transition state. Here, we study the reaction in detail using topological methods of quantum chemistry (quantum theory of atoms in molecules and electron localization function analysis) and show how electron density and chemical bonding between the atoms change in the course of the reaction.

- 1646–1656 **Theoretical study on the gas phase reaction of propargyl alcohol with hydroxyl radical** ,Yunju Zhang, Jingyu Sun, Wanqiao Zhang, Yizhen Tang , Rongshun Wang[Northeast Normal University]

The reaction of propargyl alcohol with hydroxyl radical has been studied extensively at CCSD(T)/aug-cc-pVTZ//MP2/cc-pVTZ level. This is the first time to gain a conclusive insight into the reaction mechanism and kinetics for this important reaction in detail.

- 1657–1663 **Dimetallic sulfide endohedral metallofullerene Sc₂S@C₇₆: Density functional theory characterization** ,Pei Zhao, Tao Yang, Yi-Jun Guo, Jing-Shuang Dang, Xiang Zhao[Xi'an Jiaotong University] ,Shigeru Nagase

In terms of density functional theory combined with statistic mechanics computations, we investigated a dimetallic sulfide endohedral fullerene Sc₂S@C₇₆ which has been synthesized without any characterization in experiments.

Journal of Computational Chemistry, 35 (23), August, 2014.

- 1665–1671 **Improving the calculation of magnetic coupling constants in MRPT methods** ,Mariano Spivak, Celestino Angeli, Carmen J. Calzado , Coen de Graaf [Universitat Rovira i Virgili]

The magnetic coupling in transition metal compounds with more than one unpaired electron per magnetic center has been studied with multiconfigurational perturbation theory.

- 1672–1681 **Exploring chemical reactivity of complex systems with path-based coordinates: Role of the distance metric** ,Kirill Zinovjev , Iñaki Tuñón[Universitat de València]

Path-based reaction coordinates constitute a valuable tool for free-energy calculations in complex processes. In this work, we show that, accounting for the correct metric tensor, these kind of variables can provide iso-hypersurfaces that coincide with the iso-committor surfaces and that activation free energies equal the value that would be obtained if the committor function itself were used as reaction coordinate.

- 1682–1689 **Replica exchange with guided annealing for accelerated sampling of disordered protein conformations** ,Weihong Zhang , Jianhan Chen [Kansas State University]

We critically examine a recently proposed convective replica exchange (cRE) method for enhanced sampling of protein conformation based on theoretical and numerical analysis. The results demonstrate that cRE and related replica exchange with guided annealing (RE-GA) schemes lead to unbalanced exchange attempt probabilities and break detailed balance whenever the system undergoes slow conformational transitions.

- 1690–1706 **Valence state parameters of all transition metal atoms in metalloproteins—development of ABEEM $\sigma\pi$ fluctuating charge force field** ,Zhong-Zhi Yang[Liaoning Normal University], Jian-Jiang Wang , Dong-Xia Zhao

To promote accuracy of the atom-bond electronegativity equalization method (ABEEM $\sigma\pi$) fluctuating charge polarizable force fields, and extend it to include all transition metal atoms, a new parameter, the reference charge is set up in the expression of the total energy potential function.

- 1707–1715 **Performance of density-functional tight-binding models in describing hydrogen-bonded anionic-water clusters** ,Soran Jahangiri, Lemin Cai , Gilles H. Peslherbe[Concordia University]

In this work, the reliability and accuracy of the self-consistent-charge DFTB model and its recent extension(s) in predicting the structures, binding energies, charge distributions, and vibrational frequencies of small water clusters containing polyatomic anions of the Hofmeister series have been carefully and systematically evaluated on the basis of high-level ab initio quantum-chemistry [MP2/aug-cc-pVTZ and CCSD(T)/aug-cc-pVQZ] reference data.

- 1716–1724 **Coupled-cluster frozen-density embedding using resolution of the identity methods** ,Sebastian Höfener[Karlsruher Institut für Technologie]

Frozen-density embedding (FDE) is combined with resolution of the identity (RI) Hartree–Fock and a RI-variant of a second-order approximate coupled-cluster singles and doubles (RI-CC2) to determine solvatochromic shifts for the lowest excitation energy of acetone and pyridazine, respectively, each solvated in different environments with total system sizes of about 2.5 nm diameter.

- 1725–1737 **Implementation of the diagonalization-free algorithm in the self-consistent field procedure within the four-component relativistic scheme** ,Marcela Hrdá, Tomáš Kulich, Michal Repiský, Jozef Noga, Olga L. Malkina[Comenius University],Vladimir G. Malkin

A recently developed Thouless-expansion-based diagonalization-free approach for improving the efficiency of self-consistent field (SCF) methods (Noga and Šimunek, J. Chem. Theory Comput. 2010, 6, 2706) has been adapted to the four-component relativistic scheme and implemented within the program package ReSpect.

- 1725–1737 **Implementation of the diagonalization-free algorithm in the self-consistent field procedure within the four-component relativistic scheme** ,Marcela Hrdá, Tomáš Kulich, Michal Repiský, Jozef Noga, Olga L. Malkina[Slovak Academy of Sciences] , Vladimir G. Malkin

A recently developed Thouless-expansion-based diagonalization-free approach for improving the efficiency of self-consistent field (SCF) methods (Noga and Šimunek, J. Chem. Theory Comput. 2010, 6, 2706) has been adapted to the four-component relativistic scheme and implemented within the program package ReSpect.

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About 85 Papers from more than 30 Journals are cited.

1	APPLICATIONS (56)	Page 2		
1.1	Small Molecules (11)			
	Water & Solvation	Page 2	QSAR	Page 4
	Med. Chem. And Drug Design	Page 2		
1.2	Biopolymers (43)			
	Bioinformatics and Cheminformatics	Page 5	Protein Dynamics	Page 9
	Protein Secondary Structure	Page 5	Ligand Binding	Page 11
	Protein Structure Prediction	Page 6	Enzyme Catalysis	Page 12
	Comparative or Homology Modeling	Page 6	Protein-Protein Interactions	Page 13
	Protein Sidechain Conformational	Page 7	Membrane Proteins	Page 14
	Protein Conformational Analysis	Page 7	Protein Folding	Page 16
	Protein Structure Analysis	Page 8	Nucleic Acids	Page 17
1.3	Polymers			
1.4	Surfaces, Catalysts & Material (2)	Page 17		
2	METHODOLOGY (12)	Page 34		
	QSAR	Page 18	QM & QM/MM	Page 19
	Molecular Dynamics	Page 18	Ligand Docking Modeling	Page 20
3	JOURNAL REVIEWS (4)	Page 22		
	Journal of Molecular Graphics and Modeling, 23, September, 2014.			
	Journal of Computational Chemistry, 35 (24), September, 2014.			
	Journal of Computational Chemistry, 35 (25), September, 2014.			
	Journal of Molecular Modeling, 20 (9), September, 2014.			
4	ADDRESSES OF PRINCIPAL AUTHORS	Page 33		
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1. APPLICATIONS

1.1. Small Molecules

Water AND Solvation

Coarse-Graining of TIP4P/2005, TIP4P-Ew, SPC/E, and TIP3P to Monatomic Anisotropic Water Models Using Relative Entropy Minimization

Jibao Lu, Yuqing Qiu, Riccardo Baron, Valeria Molinero
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J. Chem. Theor. and Comp, **10**, 4104–4120, 2014.

Coarse-grained models are becoming a competitive alternative for modeling processes that occur over time and length scales beyond the reach of fully atomistic molecular simulations. Ideally, coarse-grained models should not only achieve high computational efficiency but also provide accurate predictions and fundamental insight into the role of molecular interactions, the characteristic behavior, and properties of the system they model. In this work we derive a series of monatomic coarse-grained water models mXREM from the most popular atomistic water models X = TIP3P, SPC/E, TIP4P-Ew, and TIP4P/2005, using the relative entropy minimization (REM) method.

Medicinal Chemistry and Drug Design

Identification of novel leads applying *in silico* studies for Mycobacterium multidrug resistant (MMR) protein

Vasavi Malkhed, Kiran Kumar Mustyala, Sarita Rajender Potlapally, Uma Vuruputuri [Osmania University]

J. Biomol. Stru. and Dyn., **32**, 1889-1906, 2014.

Multidrug efflux mechanism is the main cause of intrinsic drug resistance in bacteria. Mycobacterium multidrug resistant (MMR) protein belongs to small multidrug resistant family proteins (SMR), causing multidrug resistance to proton (H^+)-linked lipophilic cationic drug efflux across the cell membrane. In the present work, MMR is treated as a novel target to identify new molecular entities as inhibitors for drug resistance in *Mycobacterium tuberculosis*. *In silico* techniques are applied to evaluate the 3D structure of MMR protein. The putative amino acid residues present in the active site of MMR protein are predicted.



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Medicinal Chemistry and Drug Design (Cont'd)

Affinity enhancement of HER2-binding Z(HER2:342) affibody via rational design approach: a molecular dynamics study

Mohammad Ali Ghaffari, Majid Zeinali, Ebrahim Barzegari Asadabadi, Mostafa Jamalan [Ahvaz Jundishapur University of Medical Sciences], Samad Jahandideh

J. Biomol. Stru. and Dyn., 32, 1919-1928,2014.

Human epidermal growth factor receptor 2 (HER2) contributes to the development of breast cancers and malignancies. On the other hand, engineered affibody Z(HER2:342) that binds to HER2 can be successfully used for both diagnostic purposes and specific ablation of malignant HER2-positive cell lines. In the current study, electrostatics-based prediction was applied for improving Z(HER2:342) binding affinity using computational design. The affibody Z(HER2:342) alone and in complex with HER2 was energetically minimized, solvated in explicit water, and neutralized.

Molecular dynamics and molecular docking studies on E166A point mutant, R274N/R276N double mutant, and E166A/R274N/R276N triple mutant forms of class A β -lactamases

K.M. Kumar, P. Lavanya, Anand Anbarasu , Sudha Ramaiah[VIT University]

J. Biomol. Stru. and Dyn., 32, 1953-1968,2014.

Bacterial resistance to β -lactams antibiotics is a serious threat to human health. The most common cause of resistance to the β -lactams is the production of β -lactamase that inactivates β -lactams. Specifically, class A extended-spectrum β -lactamase produced by antibiotic resistant bacteria is capable of hydrolyzing extended-spectrum Cephalosporins and Monobactams. Mutations in class A β -lactamases play a crucial role in substrate and inhibitor specificity. In this present study, the E166A point mutant, R274N/R276N double mutant, and E166A/R274N/R276N triple mutant class A β -lactamases are analyzed.

Discovery of novel anti-HIV-1 agents based on a broadly neutralizing antibody against the envelope gp120 V3 loop: a computational study

Alexander M. Andrianov, Ivan A. Kashyn , Alexander V. Tuzikov[National Academy of Sciences of Belarus]

J. Biomol. Stru. and Dyn., 32, 1993-2004,2014.

A computer-aided search for novel anti-HIV-1 agents able to mimic the pharmacophore properties of broadly neutralizing antibody (bNAbs) 3074 was carried out based on the analysis of X-ray complexes of this antibody Fab with the MN, UR29, and VI191 peptides from the V3 loop of the HIV envelope protein gp120. Using these empirical data, peptidomimetic candidates of bNAbs 3074 were identified by a public, web-oriented virtual screening platform (pepMMsMIMIC) and models of these candidates bound to the above V3 peptides were generated by molecular docking.

Development and Biological Evaluation of Potent and Selective c-KITD816V Inhibitors

Soyoung Lee, Hyunseung Lee, Jinhee Kim, Suhyun Lee, Soo Jung Kim, Byong-Seok Choi, Soon-Sun Hong, Sungwoo Hong [Korea Advanced Institute of Science and Technology (KAIST)]

J.Med.Chem., 57, 6428–6443, 2014.

The c-KIT tyrosine kinase has emerged as a potential therapeutic target for an array of diseases. However, there exists a drug resistance that is caused by mutations in c-KIT; therefore, c-KIT remains as a clinical challenge due to limited effective treatment options for therapies. For example, the acquired activating point mutation D816V significantly impairs the efficacy of targeted cancer therapies. Understanding the mechanisms of drug resistance at the molecular level will aid in designing and developing particular inhibitors with the potential to overcome these resistance mutations.

Medicinal Chemistry and Drug Design (Cont'd)

Unbinding free energy of acetylcholinesterase bound oxime drugs along the gorge pathway from metadynamics-umbrella sampling investigation

Arup K. Pathak, Tusar Bandyopadhyay [Bhabha Atomic Research Centre]

Proteins: Stru. Fun. & Bioinf., **82**, 1799–1818, 2014.

Because of the pivotal role that the nerve enzyme, acetylcholinesterase plays in terminating nerve impulses at cholinergic synapses. Its active site, located deep inside a 20 Å gorge, is a vulnerable target of the lethal organophosphorus compounds. Potent reactivators of the intoxicated enzyme are nucleophiles, such as bispyridinium oxime that binds to the peripheral anionic site and the active site of the enzyme through suitable cation- π interactions. Atomic scale molecular dynamics and free energy calculations in explicit water are used to study unbinding pathways of two oxime drugs (Ortho-7 and Obidoxime) from the gorge of the enzyme.

Substrate-mediated control of the conformation of an ancillary domain delivers a competent catalytic site for *N*-acetylneuraminic acid synthase

Dmitri D. A. Joseph, Wanting Jiao, Sarah A. Kessans, Emily J. Parker [University of Canterbury]

Proteins: Stru. Fun. & Bioinf., **82**, 2054–2066, 2014.

N-Acetylneuraminic acid (NANA) is the most common naturally occurring sialic acid and plays a key role in the pathogenesis of a select number of neuroinvasive bacteria such as *Neisseria meningitidis*. NANA is synthesized in prokaryotes via a condensation reaction between phosphoenolpyruvate and *N*-acetylmannosamine. We have investigated the role of the AFPL domain by characterizing a truncated variant of NmeNANAS, which was discovered to be soluble yet inactive.

Structural basis of valmerins as dual inhibitors of GSK3 β /CDK5

Xiaolong Li, Xiaowei Wang, Zibin Tian, Houling Zhao, Da Liang, Weisong Li, Yujin Qiu [Affiliated Hospital of Weifang Medical University], Shaoyong Lu

J. Mol.Mod., **20**, 2407, 2014.

Development of multi-target drugs is becoming increasingly attractive in the repertoire of protein kinase inhibitors discovery. In this study, we carried out molecular docking, molecular dynamics simulations, molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) binding free energy calculations, principal component analysis (PCA), and dynamical cross-correlation matrices (DCCM) to dissect the molecular mechanism for the valmerin-19 acting as a dual inhibitor for glycogen synthase kinase 3 β (GSK3 β) and cyclin-dependent kinase 5 (CDK5).

Quantitative Structure-Activity Relations

In silico screening and study of novel ERK2 inhibitors using 3D QSAR, docking and molecular dynamics

Sofiene Larif [Faculty of Medicine of Sousse], Chaker Ben Salem, Housseem Hmouda, Kamel Bouraoui

J. Mol.Graph. and Mod., **53**, 1-12 2014.

ERK2 is a dual specificity protein kinase, part of the Ras/Raf/MEK/ERK signal transduction cascade. It forms an interesting target for inhibition based on its relationship with cell proliferation and oncogenesis. A 3D QSAR pharmacophore model (Hypo1) with high correlation ($r = 0.938$) was developed for ERK2 ATP site on the basis of experimentally known inhibitors. The model included three hydrogen bonds, and one hydrophobic site. Assessment of Hypo1 through Fisher randomization, cost analysis, leave one out method and decoy test suggested that the model can reliably detect ERK2 inhibitors.

Quantitative Structure Activity Relations (Cont'd)

QSAR design of triazolopyridine mGlu2 receptor positive allosteric modulators

Gary Tresadern [A Division of Janssen Pharmaceutica NV],
José-Maria Cid, Andrés A. Trabanco

J. Mol.Graph. and Mod., **53**, 82-91, 2014.

Two QSAR approaches were applied to assist the design and to prioritise the synthesis of new active mGlu2 receptor positive allosteric modulators (PAMs). With the aim to explore a particular point of substitution the models successfully prioritised molecules originating from chemistry ideas and a large virtual library. The two methods, 3D topomer CoMFA and support vector machines with 2D ECFP6 fingerprints, delivered good correlation and success in this prospective application. Fourteen molecules with different substituent decoration were identified by the in silico models and synthesised.

1.2. Biopolymers

Bioinformatics and Cheminformatics

MoDPepInt: an interactive web server for prediction of modular domain-peptide interactions

Kousik Kundu, Martin Mann, Fabrizio Costa, Rolf Backofen[University of Freiburg]

Bioinformatics. **30**, 2668-2669, 2014.

MoDPepInt (Modular Domain Peptide Interaction) is a new easy-to-use web server for the prediction of binding partners for modular protein domains. Currently, we offer models for SH2, SH3 and PDZ domains via the tools SH2PepInt, SH3PepInt and PDZPepInt, respectively. More specifically, our server offers predictions for 51 SH2 human domains and 69 SH3 human domains via single domain models, and predictions for 226 PDZ domains across several species, via 43 multidomain models. All models are based on support vector machines with different kernel functions ranging from polynomial, to Gaussian, to advanced graph kernels.

Protein Secondary Structure

PCASSO: A fast and efficient α -based method for accurately assigning protein secondary structure elements

Sean M. Law, Aaron T. Frank, Charles L. Brooks III[University of Michigan]

J. Comp. Chem., **35**, 1757–1761, 2014.

Proteins are often characterized in terms of their primary, secondary, tertiary, and quaternary structure. Algorithms such as define secondary structure of proteins (DSSP) can automatically assign protein secondary structure based on the backbone hydrogen-bonding pattern. However, the assignment of secondary structure elements (SSEs) becomes a challenge when only the α coordinates are available. In this work, we present protein C-alpha secondary structure output (PCASSO), a fast and accurate program for assigning protein SSEs using only the α positions.

Protein Secondary Structure (Cont'd)

Driving β -Strands into Fibrils

Zhaoqian Su , Cristiano L. Dias [New Jersey Institute of Technology]

J. Phys. Chem. B., **118**, 10830–10836, 2014.

In this work we study contributions of mainchain and side chain atoms to fibrillization of polyaniline peptides using all-atom molecular dynamics simulations. We show that the total number of hydrogen bonds in the system does not change significantly during aggregation. This emerges from a compensatory mechanism where the formation of one interpeptide hydrogen bond requires rupture of two peptide–water bonds, leading to the formation of one extra water–water bond. Since hydrogen bonds are mostly electrostatic in nature, this mechanism implies that electrostatic energies related to these bonds are not minimized during fibril formation.

Protein Structure Prediction

WeFold: A coopetition for protein structure prediction

George A. Khoury, Adam Liwo, Firas Khatib, Hongyi Zhou, Gaurav Chopra, Jaume Bacardit, Leandro O. Bortot, Rodrigo A. Faccioli, Xin Deng, Yi He, Pawel Krupa, Jilong Li, Magdalena A. Mozolewska, Adam K. Sieradzan, James Smadbeck, Tomasz Wirecki, Seth Cooper, Jeff Flatten, Kefan Xu, David Baker, Jianlin Cheng, Alexandre C. B. Delbem, Christodoulos A. Floudas, Chen Keasar, Michael Levitt, Zoran Popović, Harold A. Scheraga, Jeffrey Skolnick, Silvia N. Crivelli [University of California] , Foldit Players

Proteins: Stru. Fun. & Bioinf., **82**, 1850–1868, 2014.

The protein structure prediction problem continues to elude scientists. Despite the introduction of many methods, only modest gains were made over the last decade for certain classes of prediction targets. To address this challenge, a social-media based worldwide collaborative effort, named WeFold, was undertaken by 13 labs. During the collaboration, the laboratories were simultaneously competing with each other. Here, we present the first attempt at “coopetition” in scientific research applied to the protein structure prediction and refinement problems.

Comparative or Homology Modeling

Rebuilding a macromolecular membrane complex at the atomic scale: Case of the Kir6.2 potassium channel coupled to the muscarinic acetylcholine receptor M2

Nicolas Sapay, Argel Estrada-Mondragon, Christophe Moreau, Michel Vivaudou , Serge Crouzy[Université Grenoble Alpes]

Proteins: Stru. Fun. & Bioinf., **82**, 1694–1707, 2014.

Ion channel-coupled receptors (ICCR) are artificial proteins built from a G protein-coupled receptor and an ion channel. A long protein engineering phase has led to the biochemical characterization of the M2-Kir6.2 construct. However, its molecular mechanism remains to be elucidated. In particular, it is important to determine how the activation of M2 by its agonist acetylcholine triggers the modulation of the Kir6.2 channel *via* the M2-Kir6.2 linkage. In the present study, we have developed and validated a computational approach to rebuild models of the M2-Kir6.2 chimera from the molecular structure of M2 and Kir6.2.

Protein Side-Chain Conformation Prediction

Assessment of protein side-chain conformation prediction methods in different residue environments

Lenna X. Peterson, Xuejiao Kang ,Daisuke Kihara [Purdue University]

Proteins: Stru. Fun. & Bioinf., **82**, 1971–1984, 2014.

Computational prediction of side-chain conformation is an important component of protein structure prediction. Accurate side-chain prediction is crucial for practical applications of protein structure models that need atomic-detailed resolution such as protein and ligand design. We evaluated the accuracy of eight side-chain prediction methods in reproducing the side-chain conformations of experimentally solved structures deposited to the Protein Data Bank. Prediction accuracy was evaluated for a total of four different structural environments (buried, surface, interface, and membrane-spanning) in three different protein types (monomeric, multimeric, and membrane).

Protein Confirmational Analysis

Characterizing Solution Surface Loop Conformational Flexibility of the GM2 Activator Protein

Jeffery D. Carter, Jordan D. Mathias, Edwin F. Gomez, Yong Ran, Fang Xu, Luis Galiano, Nguyen Q. Tran, Peter W. D'Amore, Christine S. Wright, Dhruva K. Chakravorty, Gail E. Fanucci [University of Florida]

J. Phys. Chem. B., **118**, 10607–10617, 2014.

GM2AP has a β -cup topology with numerous X-ray structures showing multiple conformations for some of the surface loops, revealing conformational flexibility that may be related to function, where function is defined as either membrane binding associated with ligand binding and extraction or interaction with other proteins. Here, site-directed spin labeling (SDSL) electron paramagnetic resonance (EPR) spectroscopy and molecular dynamic (MD) simulations are used to characterize the mobility and conformational flexibility of various structural regions of GM2AP.

Molecular dynamics simulation of the phosphorylation-induced conformational changes of a tau peptide fragment

Albert J. Lyons, Neha S. Gandhi , Ricardo L. Mancera[Curtin University]

Proteins: Stru. Fun. & Bioinf., **82**, 1907–1923, 2014.

Aggregation of the microtubule associated protein tau (MAPT) within neurons of the brain is the leading cause of tauopathies such as Alzheimer's disease. MAPT is a phospho-protein that is selectively phosphorylated by a number of kinases *in vivo* to perform its biological function. However, it may become pathogenically hyperphosphorylated, causing aggregation into paired helical filaments and neurofibrillary tangles. The phosphorylation induced conformational change on a peptide of MAPT (htau_{225–250}) was investigated by performing molecular dynamics simulations with different phosphorylation patterns of the peptide (pThr231 and/or pSer235) in different simulation conditions to determine the effect of ionic strength and phosphate charge.

Protein Conformational Analysis (Cont'd)

Multiple Gaussian network modes alignment reveals dynamically variable regions: The hemoglobin case

Meir Davis , Dror Tobi[Ariel University]

Proteins: Stru. Fun. & Bioinf., **82**, 2097–2105, 2014.

Gaussian network model (GNM) modes of motion are calculated to a dataset of hemoglobin (Hb) structures and modes with dynamics similarity to the T state are multiply aligned. The sole criterion for the alignment is the mode shape itself and not sequence or structural similarity. Standard deviation (SD) of the GNM value score along the alignment is calculated, regions with high SD are defined as dynamically variable. The analysis shows that the $\alpha 1\beta 1/\alpha 2\beta 2$ interface is a dynamically variable region but not the $\alpha 1\beta 2/\alpha 2\beta 1$ and the $\alpha 1\alpha 2/\beta 1\beta 2$ interfaces. The results are in accordance with the T $\rightarrow$ R2 transition of Hb.

Multiple conformational states and gate opening of outer membrane protein TolC revealed by molecular dynamics simulations

Beibei Wang, Jingwei Weng , Wenning Wang[Fudan University]

Proteins: Stru. Fun. & Bioinf., **82**, 2169–2179, 2014.

Outer membrane protein TolC serves as an exit duct for exporting substances out of cell. The occluded periplasmic entrance of TolC is required to open for substrate transport, although the opening mechanism remains elusive. In this study, systematic molecular dynamics (MD) simulations for wild type TolC and six mutants were performed to explore the conformational dynamics of TolC. The periplasmic gate was shown to sample multiple conformational states with various degrees of gating opening. The gate opening was facilitated by all mutations except Y362F, which adopts an even more closed state than wild type TolC.

Conformational analysis of glutamic acid: a density functional approach using implicit continuum solvent model

Başak Turan, Cenk Selçuki[Ege University]

J. Mol.Mod., **20**, 2396, 2014.

Amino acids are constituents of proteins which take part almost in all metabolic reactions. Glutamic acid, with an ability to form a negatively charged side chain, plays a major role in intra and intermolecular interactions of proteins, peptides, and enzymes. An exhaustive conformational analysis has been performed for all eight possible forms at B3LYP/cc-pVTZ level. All possible neutral, zwitterionic, protonated, and deprotonated forms of glutamic acid structures have been investigated in solution by using polarizable continuum model mimicking water as the solvent.

Protein Structure Analysis

Molecular simulation of Tyr105 phosphorylated pyruvate kinase M2 to understand its structure and dynamics

Ponnusamy Kalaarasan, Naidu Subbarao, Rameshwar NK Bamezai [Shri Mata Vaishno Devi University]

J. Mol.Mod., **20**, 2447, 2014.

Tyrosine phosphorylation (p-Y105) of pyruvate kinase (PK) M2, in recent years, has been suggested to facilitate Warburg effect and tumor cell growth. However, a comparison of the structural dynamics of the un-phosphorylated, the active, and the phosphorylated-at-Y105, the inactive-states, is not clear. We studied molecular dynamics of the two states to unravel these features, where phosphorylated PKM2 showed a rapid global conformation change in the initial stages of the simulation.

Protein Dynamics

Fibril Elongation by A β 17–42: Kinetic Network Analysis of Hybrid-Resolution Molecular Dynamics Simulations

Wei Han , Klaus Schulten [University of Illinois at Urbana–Champaign]

J. Am. Chem. Soc., 2013, **136**, 12450–12460, 2014.

A critical step of β -amyloid fibril formation is fibril elongation in which amyloid- β monomers undergo structural transitions to fibrillar structures upon their binding to fibril tips. The atomic detail of the structural transitions remains poorly understood. Computational characterization of the structural transitions is limited so far to short A β segments (5–10 aa) owing to the long time scale of A β fibril elongation. To overcome the computational time scale limit, we combined a hybrid-resolution model with umbrella sampling and replica exchange molecular dynamics and performed altogether ~1.3 ms of molecular dynamics simulations of fibril elongation for A β 17–42.

Minimalist Model for the Dynamics of Helical Polypeptides: A Statistic-Based Parametrization

Giulia Lia Beatrice Spampinato, Giuseppe Maccari [Istituto Nanoscienze—CNR and Scuola Normale Superiore], Valentina Tozzini

J. Chem. Theor. and Comp., **10**, 3885–3895, 2014.

Low-resolution models are often used to address macroscopic time and size scales in molecular dynamics simulations of biomolecular systems. Coarse graining is often coupled to knowledge-based parametrization to obtain empirical potentials able to reproduce the system thermodynamic behavior. Here, a minimalist coarse grained (GC) model for the helical structures of proteins is reported. A knowledge-based parametrization strategy is coupled to the explicit inclusion of hydrogen-bonding-related terms, resulting in an accurate reproduction of the structure and dynamics of each single helical type, as well as the internal conformational variables correlation.

Effects of Galactosylation in Immunoglobulin G from All-Atom Molecular Dynamics Simulations

Michael E. Fortunato , Coray M. Colina [The Pennsylvania State University]

J. Phys. Chem. B., **118**, 9844–9851, 2014.

Explicit water atomistic molecular dynamics simulations (200 ns, ~330 000 atoms) were performed to study the effects of galactosylation in the Fc domain of immunoglobulin G1. Two glycoforms were simulated to observe changes in protein–carbohydrate interactions and carbohydrate structure. A high degree of flexibility was observed in the small hinge region of the protein, while large domains remained stable. The hinge region flexibility allowed both translation and rotation of the domains relative to each other, resulting in a large number of possible conformations available.

Hydrogen Bonds and Heat Diffusion in α -Helices: A Computational Study

German Miño [Universidad de Chile], Raul Barriga, Gonzalo Gutierrez

J. Phys. Chem. B., **118**, 10025–10034, 2014.

Recent evidence has shown a correlation between the heat diffusion pathways and the known allosteric communication pathways in proteins. Allosteric communication in proteins is a central, yet unsolved, problem in biochemistry, and the study and characterization of the structural determinants that mediate energy transfer among different parts of proteins is of major importance. In this work, we characterized the role of hydrogen bonds in diffusivity of thermal energy for two sets of α -helices with different abilities to form hydrogen bonds.

Protein Dynamics (Cont'd)

Insights into the Oxygen-Based Ligand of the Low pH Component of the Cu²⁺-Amyloid- β Complex

Carlos Z. Gomez-Castro, Alberto Vela [Avenida Instituto Politécnico Nacional 2508] , Liliana Quintanar, Rafael Grande-Aztatzi, Tzonka Mineva, Annick Goursot

J. Phys. Chem. B., **118**, 10052–10064, 2014.

In spite of significant experimental effort dedicated to the study of Cu²⁺ binding to the amyloid beta (A β) peptide, involved in Alzheimer's disease, the nature of the oxygen-based ligand in the low pH component of the Cu²⁺-A β (1–16) complex is still under debate. This study reports density-functional-theory-based calculations that explore the potential energy surface of Cu²⁺-complexes including N and O ligands at the N-terminus of the A β peptide, with a focus on evaluating the role of Asp1 carboxylate in copper coordination.

Folding Molecular Dynamics Simulations Accurately Predict the Effect of Mutations on the Stability and Structure of a Vammin-Derived Peptide

Panagiotis I. Koukos , Nicholas M. Glykos [University campus]

J. Phys. Chem. B., **118**, 10076–10084, 2014.

Folding molecular dynamics simulations amounting to a grand total of 4 μ s of simulation time were performed on two peptides (with native and mutated sequences) derived from loop 3 of the vammin protein and the results compared with the experimentally known peptide stabilities and structures. The simulations faithfully and accurately reproduce the major experimental findings and show that (a) the native peptide is mostly disordered in solution, (b) the mutant peptide has a well-defined and stable structure, and (c) the structure of the mutant is an irregular β -hairpin with a non-glycine β -bulge, in excellent agreement with the peptide's known NMR structure.

Replica Exchange Monte Carlo Simulation of Human Serum Albumin–Catechin Complexes

Yunqi Li, Lijia An, Qingrong Huang [Rutgers University]

J. Phys. Chem. B., **118**, 10362–10372, 2014.

Replica exchange Monte Carlo simulation equipped with an orientation-enhanced hydrophobic interaction was utilized to study the impacts of molar ratio and ionic strength on the complex formation of human serum albumin (HSA) and catechin. Selective binding behavior was observed at low catechin to HSA molar ratio (R). Increase of catechin amount can suppress HSA self-aggregation and diminish the selectivity of protein binding sites. Strong saturation binding with short-range interactions was found to level off at around 4.6 catechins per HSA on average, while this number slowly increased with R when long-range interactions were taken into account.

Essential function of the N-termini tails of the proteasome for the gating mechanism revealed by molecular dynamics simulations

Hisashi Ishida [Japan Atomic Energy Agency]

Proteins: Stru. Fun. & Bioinf., **82**, 1985–1999, 2014.

Proteasome is involved in the degradation of proteins. Proteasome activators bind to the proteasome core particle (CP) and facilitate opening a gate of the CP, where Tyr8 and Asp9 in the N-termini tails of the CP form the ordered open gate. To understand the gating mechanism of the CP for the translocation of the substrate, four different MD simulations were carried out: ordered- and Tyr8Gly/Asp9Gly disordered-gate models of the CP complexed with an ATP-independent PA26 and ordered- and disordered-gate models of the CP complexed with an ATP-dependent PAN-like activator.

Protein Dynamics (Cont'd)

Banding 2of NMR-derived methyl order parameters: Implications for protein dynamics

Kim A. Sharp[University of Pennsylvania Perelman School of Medicine], Vignesh Kasinath ,A. Joshua Wand

Proteins: Stru. Fun. & Bioinf., **82**, 2106–2117, 2014.

Our understanding of protein folding, stability, and function has begun to more explicitly incorporate dynamical aspects. Nuclear magnetic resonance has emerged as a powerful experimental method for obtaining comprehensive site-resolved insight into protein motion. It has been observed that methyl-group motion tends to cluster into three “classes” when expressed in terms of the popular Lipari-Szabo model-free squared generalized order parameter. Here the origins of the three classes or bands in the distribution of order parameters are examined.

Molecular dynamics comparison of E. coli WrbA apoprotein and holoprotein

David Reha[Academy of Sciences of the Czech Republic], Balasubramanian Harish, Dhiraj Sinha, Zdenek Kukacka, James McSally, Olga Ettrichova, Petr Novak, Jannette Carey, Rüdiger Ettrich

J. Mol.Mod., **20**, 2400, 2014.

WrbA is a novel multimeric flavodoxin-like protein of unknown function. A recent high-resolution X-ray crystal structure of E. coli WrbA holoprotein revealed a methionine sulfoxide residue with full occupancy in the FMN-binding site, a finding that was confirmed by mass spectrometry. In an effort to evaluate whether methionine sulfoxide may have a role in WrbA function, the present analyses were undertaken using molecular dynamics simulations in combination with further mass spectrometry of the protein.

Ligand Binding/Docking

Identification and in vitro evaluation of new leads as selective and competitive glycogen synthase kinase-3 β inhibitors through ligand and structure based drug design

B.S. Darshit, B. Balaji, P. Rani, M. Ramanathan [PSG College of Pharmacy]

J. Mol.Graph. and Mod., **53**, 31-47, 2014.

Glycogen synthase kinase-3 β elicits multi-functional effects on intracellular signaling pathways, thereby making the kinase a therapeutic target in multiple pathologies. Hence, it is important to selectively inhibit GSK-3 β over structurally and biologically similar targets, such as CDK5. The current study was designed to identify and evaluate novel ATP-competitive GSK-3 β inhibitors. The study was designed to identify new leads by ligand based drug design, structure based drug design and in vitro evaluation. The best validated pharmacophore model (AADDRRR) identified using LBDD was derived from a dataset of 135 molecules.

Computational Investigation of Enthalpy–Entropy Compensation in Complexation of Glycoconjugated Bile Salts with β -Cyclodextrin and Analogs

Kasper D. Tidemand, Christian Schönbeck, René Holm, Peter Westh, Günther H. Peters[Technical University of Denmark]

J. Phys. Chem. B., **118**, 10889–10897, 2014.

The inclusion complexes of glycoconjugated bile salts with β -cyclodextrin (β -CD) and 2-hydroxypropyl- β -cyclodextrins (HP- β -CD) in aqueous solution were investigated by MD simulations to provide a molecular explanation of the experimentally observed destabilizing effect of the HP substituents. Good agreement with experimental data was found with respect to penetration depths of CDs. An increased degree of HP substitution (DS) resulted in an increased probability of blocking the cavity opening, thereby hindering the bile salt from entering CD. Further, the residence time of water molecules in the cavity increased with the DS.

Enzyme Catalysis

Inhibition and Mechanism of HDAC8 Revisited

Kai Chen, Xiaoxiao Zhang, Yun-Dong Wu, Olaf Wiest
[Peking University Shenzhen Graduate School]

J. Am. Chem. Soc., 2013, **136**, 11636–11643, 2014.

Histone deacetylases (HDACs) have found intense interest as drug targets for a variety of diseases, but there is disagreement about basic aspects of the inhibition and mechanism of HDACs. QM/MM calculations of HDAC8 including a large QM region provide a model that is consistent with the available crystal structures and structure–activity relationships of different HDAC inhibitors. The calculations support a spontaneous proton transfer from a hydroxamic acid to an active site histidine upon binding to the zinc.

Comparative analysis of binding sites of human meprins with hydroxamic acid derivative by molecular dynamics simulation study

Ankur Chaudhuri, Indrani Sarkar, Sibani Chakraborty [West Bengal State University]

J. Biomol. Stru. and Dyn., 32, 1969-1978, 2014.

Meprins are complex and highly glycosylated multi-domain enzymes that require post-translational modifications to reach full activity. Meprins are metalloproteases of the astacin family characterized by a conserved zinc-binding motif (HExxHxxGFxHExxRxDR). Human meprin- α and - β protease subunits are 55% identical at the amino acid level, however the substrate and peptide bond specificities vary markedly. Current work focuses on the critical amino acid residues in the non-primed subsites of human meprins- α and - β involved in inhibitor/ligand binding.

An Allosteric Modulator of HIV-1 Protease Shows Equipotent Inhibition of Wild-Type and Drug-Resistant Proteases

Peter M.-U. Ung, James B. Dunbar, Jr., Jason E. Gestwicki, Heather A. Carlson [University of Michigan]

J. Med. Chem., 57, 6468–6478, 2014.

NMR and MD simulations have demonstrated that the flaps of HIV-1 protease (HIV-1p) adopt a range of conformations that are coupled with its enzymatic activity. Previously, a model was created for an allosteric site located between the flap and the core of HIV-1p, called the Eye site (Biopolymers 2008, 89, 643–652). Here, results from our first study were combined with a ligand-based, lead-hopping method to identify a novel compound (NIT). NIT inhibits HIV-1p, independent of the presence of an active-site inhibitor such as pepstatin A.

A Computational Approach to Enzyme Design: Predicting ω -Aminotransferase Catalytic Activity Using Docking and MM-GBSA Scoring

Sarah Sirin, Rajesh Kumar, Carlos Martinez, Michael J. Karmilowicz, Preeyantee Ghosh, Yuriy A. Abramov, Van Martin, Woody Sherman [Schrödinger, Inc.]

J. Chem. Infor. and Mod. 54, 2334–2346, 2014.

Enzyme design is an important area of ongoing research with a broad range of applications in protein therapeutics, biocatalysis, bioengineering, and other biomedical areas; however, significant challenges exist in the design of enzymes to catalyze specific reactions of interest. Here, we develop a computational protocol using an approach that combines molecular dynamics, docking, and MM-GBSA scoring to predict the catalytic activity of enzyme variants. Our primary focuses are to understand the molecular basis of substrate recognition and binding in an S-stereoselective ω -aminotransferase (ω -AT), which naturally catalyzes the transamination of pyruvate into alanine, and to predict mutations that enhance the catalytic efficiency of the enzyme.

Enzyme Catalysis (Cont'd)

The Influence of Ser-154, Cys-113, and the Phosphorylated Threonine Residue on the Catalytic Reaction Mechanism of Pin1

Esteban Vöhringer-Martinez [Universidad de Concepción,],
Toon Verstraelen, Paul W. Ayers

J. Phys. Chem. B., **118**, 9871–9880, 2014.

Pin1 is an enzyme that specifically catalyzes the cis–trans isomerization of proline amide bonds in peptides that contain a phosphorylated threonine or serine residue in the position preceding proline. In the cell, the isomerization reaction is associated with cellular signaling and has been related to diseases such as Alzheimer and cancer. The catalytic mechanism by which Pin1 accelerates the isomerization reaction, however, is still unknown. In this study, we use molecular dynamics simulation in combination with the QM/MM methodology to disclose the influence of the residues Ser-154 and Cys-113 in the enzyme and the phosphorylated threonine residue in the peptide on the reaction mechanism.

Exploring the multiscale signaling behavior of phototropin1 from *Chlamydomonas reinhardtii* using a full-residue space kinetic Monte Carlo molecular dynamics technique

Emanuel Peter, Bernhard Dick, Ivan Stambolic ,Stephan A. Baeurle[University of Regensburg]

Proteins: Stru. Fun. & Bioinf., **82**, 2018–2040, 2014.

Devising analysis tools for elucidating the regulatory mechanism of complex enzymes has been a challenging task for many decades. It generally requires the determination of the structural-dynamical information of protein solvent systems far from equilibrium over multiple length and time scales, which is still difficult both theoretically and experimentally. To cope with the problem, we introduce a full-residue space multiscale simulation method based on a combination of the kinetic Monte Carlo and molecular dynamics techniques, in which the rates of the rate-determining processes are evaluated from a biomolecular forcefield on the fly during the simulation run by taking into account the full space of residues.

Protein-Protein Interactions

HubAlign: an accurate and efficient method for global alignment of protein–protein interaction networks

Somaye Hashemifar , Jinbo Xu[Toyota Technological
Institute at Chicago]

Bioinformatics. **30**, i438–i444, 2014.

This paper presents a novel global network alignment algorithm, denoted as HubAlign, that makes use of both network topology and sequence homology information, based upon the observation that topologically important proteins in a PPI network usually are much more conserved and thus, more likely to be aligned. HubAlign uses a minimum-degree heuristic algorithm to estimate the topological and functional importance of a protein from the global network topology information.

Protein-Protein Interactions (Cont'd)

Experimental design schemes for learning Boolean network models

Nir Atias, Michal Gershenzon, Katia Labazin, Roded Sharan[Tel Aviv University]

Bioinformatics. **30**, i445-i452, 2014.

A holy grail of biological research is a working model of the cell. Current modeling frameworks, especially in the protein-protein interaction domain, are mostly topological in nature, calling for stronger and more expressive network models. We developed novel design approaches that greedily select an experiment to be performed so as to maximize the difference or the entropy in the results it induces with respect to current best-fit models. Unique to our maximum difference approach is the ability to account for all Boolean models displaying high fit to the available data. We applied both approaches to simulated and real data from the EGFR and IL1 signaling systems in human.

Feature selection and classification of protein-protein complexes based on their binding affinities using machine learning approaches

K. Yugandhar , M. Michael Gromiha[Indian Institute of Technology Madras]

Proteins: Stru. Fun. & Bioinf., **82**, 2088–2096, 2014.

Protein-protein interactions are intrinsic to virtually every cellular process. Predicting the binding affinity of protein-protein complexes is one of the challenging problems in computational and molecular biology. In this work, we related sequence features of protein-protein complexes with their binding affinities using machine learning approaches. We set up a database of 185 protein-protein complexes for which the interacting pairs are heterodimers and their experimental binding affinities are available.

Membrane Proteins and Lipid Peptide Interactions

Interactions of Protein Kinase C- α C1A and C1B Domains with Membranes: A Combined Computational and Experimental Study

Jianing Li, Brian P. Ziemba, Joseph J. Falke, Gregory A. Voth [The University of Chicago]

J. Am. Chem. Soc., 2013, **136**, 11757–11766, 2014.

Protein kinase C- α (PKC α) has been studied widely as a paradigm for conventional PKCs, with two C1 domains (C1A and C1B) being important for the regulation and function of the kinase. However, it is challenging to explore these domains in membrane-bound environments with either simulations or experiments alone. In this work, we have combined modeling, simulations, and experiments to understand the molecular basis of the PKC α C1A and C1B domain interactions with membranes.

Coarse-grained molecular dynamics simulations of protein-ligand binding

Tatsuki Negami, Kentaro Shimizu , Tohru Terada[The University of Tokyo]

J. Comp. Chem., **35**, 1835–1845, 2014.

Coarse-grained molecular dynamics (CGMD) simulations with the MARTINI force field were performed to reproduce the protein-ligand binding processes. We chose two protein-ligand systems, the levansucrase-sugar (glucose or sucrose), and LinB-1,2-dichloroethane systems, as target systems that differ in terms of the size and shape of the ligand-binding pocket and the physicochemical properties of the pocket and the ligand. Spatial distributions of the Coarse-grained (CG) ligand molecules revealed potential ligand-binding sites on the protein surfaces other than the real ligand-binding sites.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Elucidation of Conformational States, Dynamics, and Mechanism of Binding in Human κ -Opioid Receptor Complexes

Georgios Leonis, Aggelos Avramopoulos, Ramin Ekhteiari Salmas, Serdar Durdagi, Mine Yurtsever, Manthos G. Papadopoulos [National Hellenic Research Foundation]

J.Chem. Infor. and Mod. **54**, 2294–2308, 2014.

Opioid G protein-coupled receptors (GPCRs) have been implicated in modulating pain, addiction, psychotomimesis, mood and memory, among other functions. We have employed the recently reported crystal structure of the human κ -opioid receptor (κ -OR) and performed molecular dynamics (MD), free energy, and ab initio calculations to elucidate the binding mechanism in complexes with antagonist JD1c and agonist SalA. The two systems were modeled in water and in DPPC lipid bilayers, in order to investigate the effect of the membrane upon conformational dynamics.

Impact of Ionic Liquids in Aqueous Solution on Bacterial Plasma Membranes Studied with Molecular Dynamics Simulations

Geraldine S. Lim, Jernej Zidar, Daniel W. Cheong, Stephan Jaenicke, Marco Klähn [Technology and Research, 1 Pesek Road, Jurong Island]

J. Phys. Chem. B., **118**, 10444–10459, 2014.

The impact of five different imidazolium-based ionic liquids (ILs) diluted in water on the properties of a bacterial plasma membrane is investigated using molecular dynamics (MD) simulations. Cations considered are 1-octyl-3-methylimidazolium (OMIM), 1-octyloxymethyl-3-methylimidazolium (OXMIM), and 1-tetradecyl-3-methylimidazolium (TDMIM), as well as the anions chloride and lactate. The atomistic model of the membrane bilayer is designed to reproduce the lipid composition of the plasma membrane of Gram-negative *Escherichia coli*. Spontaneous insertion of cations into the membrane is observed in all ILs.

Coarse-Grained Computational Studies of Supported Bilayers: Current Problems and Their Root Causes

Antti Lamberg, Takashi Taniguchi [Kyoto University]

J. Phys. Chem. B., **118**, 10643–10652, 2014.

The supported bilayer is an important experimental method for probing the features of lipid bilayers, yet relatively few computational studies have taken up its modeling. Using coarse-grained molecular dynamics simulations based on the MARTINI force field, we show that some of the few previous attempts employing similar methodologies are problematic, and have indeed led to erroneous conclusions. We further build a theoretical framework to see where exactly the failures of parametrization lie and suggest how these earlier results should be interpreted.

Dynamic Performance of Duolayers at the Air/Water Interface. 2. Mechanistic Insights from All-Atom Simulations

Andrew J. Christofferson, George Yiapanis, Andy H. M. Leung, Emma L. Prime, Diana N. H. Tran, Greg G. Qiao, David H. Solomon, Irene Yarovsky [RMIT University]

J. Phys. Chem. B., **118**, 10927–10933, 2014.

The novel duolayer system, comprising a monolayer of ethylene glycol mono-octadecyl ether (C18E1) and the water-soluble polymer poly(vinylpyrrolidone) (PVP), has been shown to resist forces such as wind stress to a greater degree than the C18E1 monolayer alone. This paper reports all-atom molecular dynamics simulations comparing the monolayer (C18E1 alone) and duolayer systems under an applied force parallel to the air/water interface. The simulations show that, due to the presence of PVP at the interface, the duolayer film exhibits an increase in chain tilt, ordering, and density, as well as a lower lateral velocity compared to the monolayer.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

The influenza fusion peptide promotes lipid polar head intrusion through hydrogen bonding with phosphates and N-terminal membrane insertion depth

Sébastien Légaré , Patrick Lagüe[Université Laval]

Proteins: Stru. Fun. & Bioinf., **82**, 2118–2127, 2014.

Influenza infection requires fusion between the virus envelope and a host cell endosomal membrane. The influenza hemagglutinin fusion peptide (FP) is essential to viral membrane fusion. It was recently proposed that FPs would fuse membranes by increasing lipid tail protrusion, a membrane fusion transition state. The details of how FPs induce lipid tail protrusion, however, remain to be elucidated. To decipher the molecular mechanism by which FPs promote lipid tail protrusion, we performed molecular dynamics simulations of the wild-type (WT) FP, fusogenic mutant F9A, and nonfusogenic mutant W14A in model bilayers.

Protein Folding

A collaborative visual analytics suite for protein folding research

William Harvey, In-Hee Park, Oliver Rübel, Valerio Pascucci, Peer-Timo Bremer, Chenglong Li, Yusu Wang[The Ohio State University]

J. Mol.Graph. and Mod., **53**, 59-71 , 2014.

Molecular dynamics (MD) simulation is a crucial tool for understanding principles behind important biochemical processes such as protein folding and molecular interaction. With the rapidly increasing power of modern computers, large-scale MD simulation experiments can be performed regularly, generating huge amounts of MD data. An important question is how to analyze and interpret such massive and complex data. One of the (many) challenges involved in analyzing MD simulation data computationally is the high-dimensionality of such data. Given a massive collection of molecular conformations, researchers typically need to rely on their expertise and prior domain knowledge in order to retrieve certain conformations of interest.

Exploring the Unfolding Pathway of Maltose Binding Proteins: An Integrated Computational Approach

Carlo Guardiani, Daniele Di Marino, Anna Tramontano, Mauro Chinappi, Fabio Cecconi [CNR–Istituto dei Sistemi Complessi (ISC)]

J. Chem. Theor. and Comp., **10**, 3589–3597, 2014.

Recent single-molecule force spectroscopy experiments on the Maltose Binding Proteins (MBPs) identified four stable structural units, termed unfoldons, that resist mechanical stress and determine the intermediates of the unfolding pathway. In this work, we analyze the topological origin and the dynamical role of the unfoldons using an integrated approach which combines a graph-theoretical analysis of the interaction network of the MBP native-state with steered molecular dynamics simulations.

Nucleic Acids

Modeling DNA methylation dynamics with approaches from phylogenetics

John A. Capra [Vanderbilt University] , Dennis Kostka

Bioinformatics. **30**, i408-i414, 2014.

Genome-wide DNA methylation assays have become increasingly common, and this has enabled characterization of DNA methylation in distinct stages across differentiating cellular lineages. Changes in CpG methylation are essential to cellular differentiation; however, current methods for modeling methylation dynamics do not account for the dependency structure between precursor and dependent cell types. We developed a continuous-time Markov chain approach, based on the observation that changes in methylation state over tissue differentiation can be modeled similarly to DNA nucleotide changes over evolutionary time.

Surfaces, Catalysts, and Materials Subjects

Surface–Bulk Partition of Surfactants Predicted by Molecular Dynamics Simulations

Chunwei Yang , Huai Sun [Shanghai Jiao Tong University]

J. Phys. Chem. B., **118**, 10695–10703, 2014.

The surface–bulk partition of surfactants is a piece of important information for understanding the performance of surfactants. In this work, we predicted surface–bulk partitions for three ionic surfactants (sodium hexyl sulfate, sodium nonyl sulfate, sodium dodecyl sulfate) using molecular dynamics simulations and a coarse-grained force field. The simulations were performed with the bilayer model that represents thin films. By setting initial configurations using chemical potentials calculated for infinitely dilute solutions, we obtained a sufficient number of independent samples for each simulation which ran at least 2 μ s.

Methane Aqueous Fluids in Montmorillonite Clay Interlayer under Near-Surface Geological Conditions: A Grand Canonical Monte Carlo and Molecular Dynamics Simulation Study

Qi Rao , Yongsheng Leng [The George Washington University]

J. Phys. Chem. B., **118**, 10956–10965, 2014.

The grand-canonical Monte Carlo (GCMC) and molecular dynamics (MD) simulations are performed to investigate the methane aqueous fluids in Na-montmorillonite clay interlayer under near-surface geological temperature and pressure conditions ($T = 300$ K and $P = 20$ –50 bar). The chemical potentials of water and methane under these T/P conditions are calculated using the Widom's insertion method. These chemical potentials are used in the GCMC simulations to determine the contents of different species in the clay interlayer, especially in those that correspond to the equilibrium stable spacing distances.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Integrative and Personalized QSAR Analysis in Cancer by Kernelized Bayesian Matrix Factorization

Muhammad Ammad-ud-din, Elisabeth Georgii, Mehmet Gönen, Tuomo Laitinen, Olli Kallioniemi, Krister Wennerberg, Antti Poso, Samuel Kaski [Aalto University]

J.Chem. Infor. and Mod. **54**, 2347–2359, 2014.

With data from recent large-scale drug sensitivity measurement campaigns, it is now possible to build and test models predicting responses for more than one hundred anticancer drugs against several hundreds of human cancer cell lines. We extend this line of research in two directions: (1) an integrative QSAR approach predicting the responses to new drugs for a panel of multiple known cancer cell lines simultaneously and (2) a personalized QSAR approach predicting the responses to new drugs for new cancer cell lines. To solve the modeling task, we apply a novel kernelized Bayesian matrix factorization method.

Molecular Dynamics

Functional Dynamics of Hexameric Helicase Probed by Hydrogen Exchange and Simulation

Gaël Radou, Frauke N. Dreyer, Roman Tuma, Emanuele Paci [University of Leeds]

Biophysical Journal. **107**, 983-990, 2014.

The biological function of large macromolecular assemblies depends on their structure and their dynamics over a broad range of timescales; for this reason, it is a significant challenge to investigate these assemblies using conventional experimental techniques. One of the most promising experimental techniques is hydrogen-deuterium exchange detected by mass spectrometry. Here, we describe to our knowledge a new computational method for quantitative interpretation of deuterium exchange kinetics and apply it to a hexameric viral helicase P4 that unwinds and translocates RNA into a virus capsid at the expense of ATP hydrolysis.

Reaction analysis and visualization of ReaxFF molecular dynamics simulations

Jian Liu, Xiaoxia Li, Li Guo, Mo Zheng, Junyi Han, Xiaolong Yuan, Fengguang Nie, Xiaolong Liu [Chinese Academy of Sciences]

J. Mol.Graph. and Mod., **53**, 13-22, 2014.

ReaxFF MD (Reactive Force Field Molecular Dynamics) is a promising method for investigating complex chemical reactions in relatively larger scale molecular systems. The existing analysis tools for ReaxFF MD lack the capability of capturing chemical reactions directly by analyzing the simulation trajectory, which is critical in exploring reaction mechanisms. This paper presents the algorithms, implementation strategies, features, and applications of VARxMD, a tool for Visualization and Analysis of Reactive Molecular Dynamics. VARxMD is dedicated to detailed chemical reaction analysis and visualization from the trajectories obtained in ReaxFF MD simulations.

Molecular Dynamics (Cont'd)

CHARMM Force-Fields with Modified Polyphosphate Parameters Allow Stable Simulation of the ATP-Bound Structure of Ca²⁺-ATPase

Yasuaki Komuro, Suyong Re, Chigusa Kobayashi, Eiro Muneyuki, Yuji Sugita [Chuo University]

J. Chem. Theor. and Comp., **10**, 4133–4142, 2014.

Adenosine triphosphate (ATP) is an indispensable energy source in cells. In a wide variety of biological phenomena like glycolysis, muscle contraction/relaxation, and active ion transport, chemical energy released from ATP hydrolysis is converted to mechanical forces to bring about large-scale conformational changes in proteins. Investigation of structure–function relationships in these proteins by molecular dynamics (MD) simulations requires modeling of ATP in solution and ATP bound to proteins with accurate force-field parameters. In this study, we derived new force-field parameters for the triphosphate moiety of ATP based on the high-precision quantum calculations of methyl triphosphate.

Zn²⁺ Effect on Structure and Residual Hydrophobicity of Amyloid β -Peptide Monomers

Hu Shi, Baotao Kang, Jin Yong Lee [Sungkyunkwan University]

J. Phys. Chem. B., **118**, 10355–10361, 2014.

The aggregation of amyloid β -peptide (A β peptide) has been associated with the pathogenesis of Alzheimer's disease (AD). We aimed to disclose how Zn²⁺ affects the A β aggregation in detail. Thus, molecular dynamics simulation was implemented to elucidate the changes of structure and residual hydrophobicity upon Zn²⁺ coordination. Our results show that Zn²⁺ can strongly influence the structural properties of A β 40 and A β 42 by reducing helical formation and increasing turn formation to expose the hydrophobic regions.

QM and QM/MM

QM/MM Model of the Mouse Olfactory Receptor MOR244-3 Validated by Site-Directed Mutagenesis Experiments

Sivakumar Sekharan [Yale University], Mehmed Z. Ertem, Hanyi Zhuang, Eric Block, Hiroaki Matsunami, Ruina Zhang, Jennifer N. Wei, Yi Pan, Victor S. Batista

Biophysical Journal. **107**, L5–L8, 2014.

Understanding structure/function relationships of olfactory receptors is challenging due to the lack of x-ray structural models. Here, we introduce a QM/MM model of the mouse olfactory receptor MOR244-3, responsive to organosulfur odorants such as (methylthio)methanethiol. The binding site consists of a copper ion bound to the heteroatoms of amino-acid residues H105, C109, and N202. The model is consistent with site-directed mutagenesis experiments and biochemical measurements of the receptor activation, and thus provides a valuable framework for further studies of the sense of smell at the molecular level.

Molecular dynamics simulations of ion solvation by flexible-boundary QM/MM: On-the-fly partial charge transfer between QM and MM subsystems

Soroosh Pezeshk, Hai Lin [University of Colorado Denver]

J. Comp. Chem., **35**, 1778–1788, 2014.

The flexible-boundary (FB) QM/MM scheme accounts for partial charge transfer between the QM and MM subsystems. Previous calculations have demonstrated excellent performance of FB-QM/MM in geometry optimizations. This article reports an implementation to extend FB-QM/MM to molecular dynamics simulations. To prevent atoms from getting unreasonably close, which can lead to polarization catastrophe, empirical correcting functions are introduced to provide additive penalty energies for the involved atom pairs and to improve the descriptions of the repulsive exchange forces in FB-QM/MM calculations.

QM and QM/MM (Cont'd)

DFT study of the per-6-amino- β -cyclodextrin as catalyst in synthesis of 2-aryl-2,3-dihydro-4-quinolones

Yali Wan, Xueye Wang[Xiangtan University] , Na Liu

J. Mol.Mod., **20**, 2431, 2014.

The synthesis of 2-aryl-2,3-dihydro-4-quinolones in the presence of per-6-amino- β -cyclodextrin (per-6-ABCD) as catalyst can improve selectivity and yield. The interaction between per-6-ABCD and benzaldehyde or o-aminoacetophenone plays an important role in this reaction. This paper studies the complexes of per-6-ABCD with benzaldehyde and o-aminoacetophenone using density functional theory (DFT) method. The reaction process is investigated by studying the energy of the reactants and the product.

Ligand Docking

Including ligand-induced protein flexibility into protein tunnel prediction

Laura J. Kingsley , Markus A. Lill [Purdue University]

J. Comp. Chem., **35**, 1748–1756, 2014.

In proteins with buried active sites, understanding how ligands migrate through the tunnels that connect the exterior of the protein to the active site can shed light on substrate specificity and enzyme function. A growing body of evidence highlights the importance of protein flexibility in the binding site on ligand binding; however, the influence of protein flexibility throughout the body of the protein during ligand entry and egress is much less characterized. We have developed a novel tunnel prediction and evaluation method named IterTunnel, which includes the influence of ligand-induced protein flexibility, guarantees ligand egress, and provides detailed free energy information as the ligand proceeds along the egress route.

Ligand–Receptor Affinities Computed by an Adapted Linear Interaction Model for Continuum Electrostatics and by Protein Conformational Averaging

Ariane Nunes-Alves , Guilherme Menegon Arantes [Instituto de Química, Universidade de São Paulo]

J.Chem. Infor. and Mod. **54**, 2309–2319, 2014.

Accurate calculations of free energies involved in small-molecule binding to a receptor are challenging. Interactions between ligand, receptor, and solvent molecules have to be described precisely, and a large number of conformational microstates has to be sampled, particularly for ligand binding to a flexible protein. Linear interaction energy models are computationally efficient methods that have found considerable success in the prediction of binding free energies. Here, we parametrize a linear interaction model for implicit solvation with coefficients adapted by ligand and binding site relative polarities in order to predict ligand binding free energies.

Ligand Docking (Cont'd)

Cation- π , amino- π , π - π , and H-bond interactions stabilize antigen-antibody interfaces

Georgios A. Dalkas, Fabian Teheux, Jean Marc Kwasigroch ,
Marianne Rooman[Université Libre de Bruxelles]

Proteins: Stru. Fun. & Bioinf., **82**, 1734–1746, 2014.

The identification of immunogenic regions on the surface of antigens, which are able to stimulate an immune response, is a major challenge for the design of new vaccines. Computational immunology aims at predicting such regions—in particular B-cell epitopes—but is far from being reliably applicable on a large scale. To gain understanding into the factors that contribute to the antigen-antibody affinity and specificity, we perform a detailed analysis of the amino acid composition and secondary structure of antigen and antibody surfaces, and of the interactions that stabilize the complexes, in comparison with the composition and interactions observed in other heterodimeric protein interfaces.

Incorporating replacement free energy of binding-site waters in molecular docking

Hanzi Sun, Lifeng Zhao, Shiming Peng , Niu Huang
[Zhongguancun Life Science Park]

Proteins: Stru. Fun. & Bioinf., **82**, 1765–1776, 2014.

Binding-site water molecules play a crucial role in protein-ligand recognition, either being displaced upon ligand binding or forming water bridges to stabilize the complex. However, rigorously treating explicit binding-site waters is challenging in molecular docking, which requires to fully sample ensembles of waters and to consider the free energy cost of replacing waters. Here, we describe a method to incorporate structural and energetic properties of binding-site waters into molecular docking. We first developed a solvent property analysis (SPA) program to compute the replacement free energies of binding-site water molecules by post-processing molecular dynamics trajectories obtained from ligand-free protein structure simulation in explicit water.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 53, September, 2014.

- 1-12 **In silico screening and study of novel ERK2 inhibitors using 3D QSAR, docking and molecular dynamics** ,Sofiene Larif [Faculty of Medicine of Sousse], Chaker Ben Salem, Housseem Hmouda, Kamel Bouraoui

See Applications / QSAR.

- 13-22 **Reaction analysis and visualization of ReaxFF molecular dynamics simulations** ,Jian Liu, Xiaoxia Li, Li Guo, Mo Zheng, Junyi Han, Xiaolong Yuan, Fengguang Nie, Xiaolong Liu[Chinese Academy of Sciences]

See Methodology / Molecular Dynamics.

- 23-30 **Theoretical studies on kinetics, mechanism and thermochemistry of gas-phase reactions of HFE-449mec-f with OH radicals and Cl atom** ,Ramesh Chandra Deka, Bhupesh Kumar Mishra[Tezpur University]

A theoretical study on the mechanism and kinetics of the gas phase reactions of CF₃CHF₂CF₂OCH₂CF₃(HFE-449mec-f) with the OH radicals and Cl atom have been performed using meta-hybrid modern density functional M06-2X using 6-31+G(d,p) basis set.

- 31-47 **Identification and in vitro evaluation of new leads as selective and competitive glycogen synthase kinase-3 β inhibitors through ligand and structure based drug design** ,B.S. Darshit, B. Balaji, P. Rani, M. Ramanathan [PSG College of Pharmacy]

See Applications / Ligand Binding.

- 48-58 **Interaction energy analysis on specific binding of influenza virus hemagglutinin to avian and human sialosaccharide receptors: Importance of mutation-induced structural change** ,Satoshi Anzaki, Chiduru Watanabe, Kaori Fukuzawa, Yuji Mochizuki, Shigenori Tanaka[Kobe University]

On the basis of available molecular structures registered in Protein Data Bank, we have theoretically carried out the interaction energy analysis for the complexes of influenza virus hemagglutinin (HA) proteins and sialosaccharide receptor analogs of host cells.

- 59-71 **A collaborative visual analytics suite for protein folding research** ,William Harvey, In-Hee Park, Oliver R  bel, Valerio Pascucci, Peer-Timo Bremer, Chenglong Li, Yusu Wang[The Ohio State University]

See Applications / Protein Folding.

- 72-81 **Skeleton-based shape analysis of protein models** ,Zhong Li[Zhejiang Sci-Tech University], Shengwei Qin, Zeyun Yu, Yao Jin

In order to compare the similarity between two protein models, a shape analysis algorithm based on skeleton extraction is presented in this paper.

- 82-91 **QSAR design of triazolopyridine mGlu2 receptor positive allosteric modulators** ,Gary Tresadern [A Division of Janssen Pharmaceutica NV], José-Maria Cid, Andrés A. Trabanco

See Applications / QSAR.

- 92-99 **Analysis of the structure and morphology of fenoxycarb crystals** ,Jacek Zeglinski[University of Limerick], Michael Svård, Jolanta Karpinska, Manuel Kuhs, Åke C. Rasmuson

In this paper, we have explored the relationship between surface structure and crystal growth and morphology of fenoxycarb (FC). Experimental vs. predicted morphologies/face indices of fenoxycarb crystals are presented.

Journal of Computational Chemistry, 35 (24), September, 2014.

- 1739–1747 **Red and blue shifted hydridic bonds** ,Miroslaw Jabłoński [Nicolaus Copernicus University]

By performing MP2/aug-cc-pVTZ *ab initio* calculations for a large set of dimer systems possessing a R—H hydridic bond involved in diverse types of intermolecular interactions (dihydrogen bonds, hydride halogen bonds, hydride hydrogen bonds, and charge-assisted hydride hydrogen bonds), we show that this is rather an elongation than a shortening that a hydride bond undergoes on interaction.

- 1748–1756 **Including ligand-induced protein flexibility into protein tunnel prediction** ,Laura J. Kingsley , Markus A. Lill [Purdue University]

See Methodology / Ligand Binding.

- 1757–1761 **PCASSO: A fast and efficient C α -based method for accurately assigning protein secondary structure elements** ,Sean M. Law, Aaron T. Frank ,Charles L. Brooks III[University of Michigan]

See Applications / Protein Secondary Structure.

- 1762–1777 **DFT assessment of the spectroscopic constants and absorption spectra of neutral and charged diatomic species of group 11 and 14 elements** ,Athanasios C. Tsepis [University of Ioannina]

The spectroscopic constants and absorption spectra of neutral and charged diatomic molecules of group 11 and 14 elements formulated as $[M_2]^{+/0/-}$ (M = Cu, Ag, Au), and $[E_2]^{+/0/-}$ (E = C, Si, Ge, Sn, Pb) have been calculated at the PBE0/Def2-QZVPP level of theory.

- 1778–1788 **Molecular dynamics simulations of ion solvation by flexible-boundary QM/MM: On-the-fly partial charge transfer between QM and MM subsystems** ,Soroosh Pezeshk, Hai Lin[University of Colorado Denver]

See Methodology / QM and QM/MM.

- 1789–1800 **Benchmarking dispersion and geometrical counterpoise corrections for cost-effective large-scale DFT calculations of water adsorption on graphene** ,Marco Lorenz, Bartolomeo Civalleri [Università di Torino], Lorenzo Maschio, Mauro Sgroi ,Daniele Pullini

The physisorption of water on graphene is investigated with the hybrid density functional theory (DFT)-functional B3LYP combined with empirical corrections, using moderate-sized basis sets such as 6-31G(d). This setup allows to model the interaction of water with graphene going beyond the quality of classical or semiclassical simulations, while still keeping the computational costs under control.

- 1801–1807 **CAST: A new program package for the accurate characterization of large and flexible molecular systems** ,Christoph Grebner, Johannes Becker, Daniel Weber, Daniel Bellinger, Maxim Tafipolski, Charlotte Brückner , Bernd Engels [Julius-Maximilians-Universität Würzburg]

The presented program package, Conformational Analysis and Search Tool (CAST) allows the accurate treatment of large and flexible (macro) molecular systems. For the determination of thermally accessible minima CAST offers the newly developed TabuSearch algorithm, but algorithms such as Monte Carlo (MC), MC with minimization, and molecular dynamics are implemented as well

Journal of Computational Chemistry, 35 (25), September, 2014.

- 1809–1814 **Basis set error estimation for DFT calculations of electronic g-tensors for transition metal complexes** ,Morten N. Pedersen [University of Southern Denmark], Erik D. Hedegård , Jacob Kongsted

We present a detailed study of the basis set dependence of electronic g-tensors for transition metal complexes calculated using Kohn–Sham density functional theory. Focus is on the use of locally dense basis set schemes where the metal is treated using either the same or a more flexible basis set than used for the ligand sphere.

- 1815–1823 **CCSD-CTOCD static dipole shielding polarizability for quantification of the chiral NMR effects in oxaziridine derivatives** ,Stefano Pelloni , Inmaculada García Cuesta[Universidad de Valencia]

Chiral discrimination by nuclear magnetic resonance (NMR) spectroscopy might be achieved through the pseudo-scalar derived from the dipole shielding polarizability tensor. Coupled Cluster Singles and Doubles-Quadratic Response (CCSD-QR) calculations inside the continuous translation of the origin of the current density formalism have been carried out to determine the effects of basis set, electron correlation, and gauge translation on the determination of this magnitude in oxaziridine derivatives.

- 1824–1834 **Shape-based virtual screening with volumetric aligned molecular shapes** ,David Ryan Koes [University of Pittsburgh] , Carlos J. Camacho

Shape-based virtual screening is an established and effective method for identifying small molecules that are similar in shape and function to a reference ligand. We describe a new method of shape-based virtual screening, volumetric aligned molecular shapes (VAMS). VAMS uses efficient data structures to encode and search molecular shapes.

- 1835–1845 **Coarse-grained molecular dynamics simulations of protein–ligand binding** ,Tatsuki Negami, Kentaro Shimizu , Tohru Terada[The University of Tokyo]

See Applications / Membrane Proteins and Lipid Peptide Interactions.

- 1846–1853 **To be or not to be butterfly: New mechanistic insights in the Aza-Michael asymmetric addition of lithium (R)-N-benzyl-N-(α -methylbenzyl)amide** ,Carlos T. Nieto, David Díez ,Narciso M. Garrido[Universidad de Salamanca]

The asymmetric Aza-Michael addition of homochiral lithium benzylamides to α,β -unsaturated esters represents an extended protocol to obtain enantioenriched β -amino esters. An exhaustive mechanistic revision of the originally proposed mechanism is reported, developing a quantum mechanics/molecular mechanics protocol for the asymmetric Aza-Michael reaction of homochiral lithium benzylamides.

- 1854–1864 **Factors affecting the computation of the ^{13}C shielding in disaccharides** ,Pablo G. Garay ,Osvaldo A. Martin ,Harold A. Scheraga , Jorge A. Vila[Cornell University]

Knowledge of the three-dimensional structures of glycans and glycoproteins is useful for a full understanding of molecular processes in which glycans are involved, such as antigen-recognition and virus infection, to name a few. To answer such questions, we performed a series of analyses on low-energy conformations, obtained by sampling the glycosidic torsional angles (ϕ , ψ) every 10° , of 12 disaccharides.

- 1865–1881 **Looking for some free energy? Call JEFREE (...)** ,Mirco Zerbetto [Università degli Studi di Padova], Andrea Piserchia , Diego Frezzato

In this communication, we present the Jarzynski's Equality FREe Energy (JEFREE) library, an efficient and easy-to-use C++ library targeted to the calculation of the free energy profile along a selected generalized coordinate of a system, within the framework of the nonequilibrium steered transformations as introduced by Jarzynski [Phys. Rev. E, 1997, 56, 5018].

Journal of Molecular Modeling, 20 (9), September, 2014.

- 2449 **Thermochemical and kinetics studies of the $\text{CH}_3\text{SH}+\text{S} (^3\text{P})$ hydrogen abstraction and insertion reactions** ,Daniely V. V. Cardoso, Leonardo A. Cunha, Rene F. K. Spada, Luiz F. A. Ferrão, Orlando Roberto-Neto, Francisco B. C. Machado[Instituto Tecnológico de Aeronáutica]

Sulfur-containing molecules have a significant impact on atmosphere and biosphere. In this work we studied, from the point of view of electronic structure and chemical kinetics methods, the elementary reactions between a methanethiol molecule and a sulfur atom leading to hydrogen abstraction C-S bond cleavage ($\text{CH}_3\text{SH}+\text{S}$; R1: $\rightarrow \text{CH}_3\text{S}+\text{SH}$; R2: $\rightarrow \text{CH}_2\text{SH}+\text{SH}$; R3: $\rightarrow \text{CH}_3+\text{HS}_2$).

- 2448 **Comparative density functional theory based study of the reactivity of Cu, Ag, and Au nanoparticles and of (111) surfaces toward CO oxidation and NO₂ reduction** ,B. Pascucci, G. S. Otero, P. G. Belelli, F. Illas, M. M. Branda [Universidad Nacional del Sur]

The reactivity of Cu, Ag, and Au nanoparticles and of the corresponding (111) surfaces of these elements toward CO oxidation and NO₂ reduction has been investigated by means of DFT and DFT-D calculations.

- 2447 **Molecular simulation of Tyr105 phosphorylated pyruvate kinase M2 to understand its structure and dynamics** ,Ponnusamy Kalaarasan, Naidu Subbarao, Rameshwar NK Bamezai [Shri Mata Vaishno Devi University]

See Applications / Protein Structure Analysis.

- 2444 **Theoretical investigation on the atmospheric fate of CF₃C(O)OCH₂O radical: alpha-ester rearrangement vs oxidation at 298 K** ,Bhupesh Kumar Mishra [Tezpur University Tezpur]

A theoretical study on the mechanism of the thermal decomposition of CF₃C(O)OCH₂O radical is presented for the first time. Geometry optimization and frequency calculations were performed at the MPWB1K/6-31 + G(d, p) level of theory and energetic information further refined by calculating the energy of the species using G2(MP2) theory.

- 2441 **Quantum chemical studies on three novel 1,2,4-triazole N-oxides as potential insensitive high explosives** ,Qiong Wu, Weihua Zhu [Nanjing University of Science and Technology], Heming Xiao

Three novel explosives were designed by introducing N-oxides into 1,2,4-triazole: 1-amino-3,5-dinitro-1,2,4-triazole-2 N-oxide (ADT2NO), 1-amino-2,5-dinitro-1,2,4-triazole-3 N-oxide (ADT3NO), and 1-amino-3,5-dinitro-1,2,4-triazole-4 N-oxide (ADT4NO).

- 2439 **Theoretical investigation on the selective detection of SO₂ molecule by AlN nanosheets** ,Somayeh. F. Rastegar [Islamic Azad University], Nasser L. Hadipour, Hamed Soleymanabadi

Theoretical calculations focused on the ability of an AlN nanosheet to detect O₃ and SO₂ molecules based on the dispersion corrected B3LYP (B3LYP-D) and B97D density functionals. Equilibrium geometries, stabilities, and the electronic properties of O₃ and SO₂ adsorptions on the surface of an AlN sheet were explored.

- 2436 **Substituent effects on cooperativity of pnictogen bonds** , Mehdi D. Esrafil [University of Maragheh], Mojhgah Ghanbari, Fariba Mohammadian-Sabet

Substituent effects on cooperativity of P...N pnictogen bonds are studied in XH₂P...NCH₂P...NCY (X=F, Cl; Y=H, F, CN, OH, NH₂) complexes using high-level ab initio calculations.

- 2435 **The reaction mechanisms and kinetics of CF₃CHFOCH₃ and CHF₂CHFOCF₃ with atomic chlorine: a computational study** ,Fang-Yu Liu, Zheng-Wen Long, Xing-Feng Tan, Bo Long [Guizhou MinZu University]

Due to their lack of effect on the ozone depletion, hydrofluoroethers are considered as potential candidates for third generation refrigerants. In the present work, the mechanisms and kinetics of reaction of the Cl atom with CF₃CHFOCH₃ and CHF₂CHFOCF₃ were investigated theoretically using quantum chemical methods and transition state theory.

- 2434 **Theoretical study of structure and stability of small gadolinium carboxylate complexes in liquid scintillator solvents** ,Pin-Wen Huang [Zhejiang University of Water Resources and Electric Power]

The structural properties of three small gadolinium carboxylate complexes in three liquid scintillator solvents (pseudocumene, linear alkylbenzene, and phenyl xylene) were theoretically investigated using density functional theory (B3LYP/LC-RECP) and polarizable continuum model (PCM).

- 2431 **DFT study of the per-6-amino- β -cyclodextrin as catalyst in synthesis of 2-aryl-2,3-dihydro-4-quinolones** ,Yali Wan, Xueye Wang[Xiangtan University] , Na Liu

See Methodology / QM and QM/MM.

- 2430 **Study of the chelating properties of $\text{Ge}(\text{OH})_2$ functionality as metal binding group for Zn^{2+} cation in simplified protease-like environments: a DFT analysis** ,Pilar Gema Rodríguez Ortega, Manuel Montejo, Juan Jesús López González [University of Jaén, Campus “Las Lagunillas”]

The development of protease's inhibitors is an active field of research in the pharmaceutical industry. As concerns the design of new inhibitors, the theoretical study of the binding patterns and energies of known metal binding groups (MBGs) toward Zn^{2+} using quantum-chemical calculations may offer a better understanding of their interaction models and may be useful for the improvement and design of novel ZBGs. Here the properties of gem- $\text{Ge}(\text{OH})_2$ -based compounds as ZBG were assessed theoretically using DFT calculations.

- 2429 **Construction and conformational behavior of peptoids with cis-amide bond geometry: design of a peptoid with alternate ϕ , ψ values of inverse PP-II/PP-II and PP-I structures** ,Fateh Singh Nandel[Panjab University], Radhika Rani Jaswal, Avneet Saini, Vibhuti Nandel, Mohd Shafique

In peptoids due to the absence of amide protons, the backbone is devoid of hydrogen bond donor, linked by tertiary amide, which can be iso-energetic between cis and trans-amide bond geometry. The peptoids can be realized with cis amide bond if the side chain of ith residue can engage the carbonyl group of ith-1 residue in CH--O interactions.

- 2428 **Rational design of carbonitrile-carboxaldehyde cation receptor models: probing the nature of the heteroatom-metal interaction** ,Ahmad Nazmi Rosli, Maizathul Akmal Abu Bakar, Vannajan Sanghiran Lee, Sharifuddin Md Zain,Mohd Rais Ahmad, Ninie Suhana Abdul Manan, Yatimah Alias, Pei Meng Woi[University of Malay]

In this work, hybrid functional and G4 methods were employed in the rational design of carbonitrile-carboxaldehyde receptor models for cation recognition.

- 2427 **$\text{B}_2(\text{BO})_6^{0/-}$ and $\text{B}_2(\text{BS})_6^{0/-}$ doubly bridged structures containing BO or BS as ligands** ,Da-Zhi Li, Si-Dian Li [Shanxi University]

The investigation on the geometrical and electronic properties of $\text{B}_2(\text{BO})_6^{0/-}$ and $\text{B}_2(\text{BS})_6^{0/-}$ has been performed by density functional theory (DFT) using the B3LYP and BP86 methods.

- 2426 **Accuracy of density functionals in the description of dispersion interactions and IR spectra of phosphates and phosphorylated compounds** ,Ashwani Sharma, Gilles Ohanessian, Carine Clavaguéra [Ecole Polytechnique]

The performances of quantum chemistry methods (i.e., DFT and ab initio) in calculating the structural and vibrational properties of phosphates and phosphorylated compounds have been evaluated.

- 2425 **Evidence of a long C-C attractive interaction in cerussite mineral: QTAIM and ELF analyses** ,Isaac Vidal Universidad de Granada], Antonio Sánchez Navas

Cerussite, an orthorhombic lead carbonate mineral, has a structure and physical properties that cannot be understood merely in terms of ionic anion-cation interactions. The nature of the chemical bonding in cerussite is analyzed by means of the quantum theory of atoms in molecules (QTAIM) and the analysis of the electron localization function (ELF).

- 2424 **Investigations into the nature of halogen- and hydrogen-bonding interactions of some heteroaromatic rings with dichlorine monoxide** ,Junyong Wu [Taizhou University]

We have studied the structures, properties, and nature of halogen- and hydrogen-bonding interactions between some heteroaromatic rings (C_5H_5N , C_4H_4O , and C_4H_4S) with Cl_2O at the MP2/aug-cc-pVTZ level.

- 2423 **Effect of electric field on the microcosmic properties of cation compound containing 2,2,6,6-tetramethyl-1-piperidinyloxy and imidazole unit** ,Shu-Cai Mao [Zhongkai University of Agriculture and Engineering], Guo-Qiang Yin, Kang-Cheng Zheng

A theoretical study of the electric-field effect on the electronic structures and related properties of the cation compound containing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and imidazole unit has been carried out, using the density functional theory (DFT) at the (U) B3LYP/6-31+G(d,p) level.

- 2422 **An assessment to evaluate the validity of different methods for the description of some corrosion inhibitors** ,M. M. Aboelnga[University of Windsor], M. K. Awad, J. W. Gauld, M. R. Mustafa

New research and development efforts using computational chemistry in studying an assessment of the validity of different quantum chemical methods to describe the molecular and electronic structures of some corrosion inhibitors were introduced.

- 2421 **Growth analysis of sodium-potassium alloy clusters from 7 to 55 atoms through a genetic algorithm approach** ,M. X. Silva, B. R. L. Galvão, J. C. Belchior [Universidade Federal de Minas Gerais,]

The potential energy hypersurface associated with sodium-potassium alloy clusters is explored via an enhanced genetic algorithm, where two different operators are added to the standard evolutionary procedure.

- 2419 **Theoretical investigation of the mechanisms and dynamics of the reaction $CHF_2OCF_2CHFCl+Cl$** ,Fengyang Bai, Yanqiu Sun, Xu Wang, Ziman Jia, Rongshun Wang, Xiumei Pan [Northeast Normal University]

The reaction of CHF_2OCF_2CHFCl with atomic chlorine was studied using B3LYP/6-311G(d,p), BHandHLYP/6-311G(d,p), and M06-2X/6-311G(d,p) methods and further using CCSD(T) and QCISD(T) methods.

- 2417 **Core-dependent and ligand-dependent relativistic corrections to the nuclear magnetic shieldings in $MH_{4-n}Y_n$ ($n = 0-4$; $M = Si, Ge, Sn$, and $Y = H, F, Cl, Br, I$) model compounds**, Alejandro F. Maldonado [Northeastern University of Argentina], Gustavo A. Aucar, Juan I. Melo

The nuclear magnetic shieldings of Si, Ge, and Sn in $MH_{4-n}Y_n$ ($M = Si, Ge, Sn$; $Y = F, Cl, Br, I$ and $n = 1-4$) molecular systems are highly influenced by the substitution of one or more hydrogens by heavy-halogen atoms. We applied the linear response elimination of small components (LRESC) formalism to calculate those shieldings and learn whether including only a few of the leading relativistic correction terms is sufficient to be able to quantitatively reproduce the full relativistic value.

- 2416 **Accesses to electronic structures and the excited states of blue luminescent copper(I) complexes containing N-heterocyclic carbene ligands: a DFT/TDDFT exploitation**, Qiang Li, Feng Zhao [Jiangxi Science and Technology Normal University], Shengxian Xu, Hongying Xia, Jinglan Wang, Yibo Wang

The ground electronic states and photophysical properties of three designed Cu(I) complexes $[Cu(ImNHC)(POP)]^+$ (1), $[Cu(methyl-ImNHC)(POP)]^+$ (2), and $[Cu(BenzImNHC)(POP)]^+$ (3); where $[ImNHC = 3\text{-methyl-1-(pyridin-2-yl)-1H-imidazol-2-ylidene}$; $methyl-ImNHC = 3\text{-methyl-1-(pyridin-2-ylmethyl)-1H-imidazol-2-ylidene}$; $BenzImNHC = 3\text{-methyl-1-(pyridin-2-yl)-1H-benzimidazol-2-ylidene}$], have been investigated using density functional theory (DFT) and time-dependent density functional theory (TDDFT).

- 2415 **The Effect of the different spin multiplicity on nonlinear optical properties of lithium decahydroborate dimers**, Yong Li, Hong-Liang Xu [Northeast Normal University], Rong-Lin Zhong, Shi-Ling Sun

In 2009, an innovative type of lithium decahydroborate ($Li@B_{10}H_{14}$) complex with a basketlike complexant of decaborane ($B_{10}H_{14}$) was designed and studied. In the present work, an unusual $Li@B_{10}H_{14}$ dimer with different spin multiplicities was designed theoretically to explore the influence of the spin multiplicity on NLO properties: 1 (triplet), 2 (open-shell singlet) and 3 (singlet).

- 2414 **Computational investigation of interaction of polypyrrole on the surface of single-walled carbon nanotube**, Manoj K. Shukla [US Army Engineer Research and Development Center], Veera Boddu, Frances Hill

A density functional theory investigation of adsorption of monomer, dimer and trimer forms of pyrrole on the outer surface of zigzag (7,0) single-walled carbon nanotube (SWCNT) has been reported. Geometries of the complexes were optimized using the M06-2X functional and the 6-31G(d,p) basis set.

- 2413 **Structural and dynamical properties of Li^+ -dibenzo-18-crown-6(DB18C6) complex in pure solvents and at the aqueous-organic interface**, Pooja Sahu, Sk. M. Ali, Jayant K. Singh [Indian Institute of Technology Kanpur]

Microstructure of dibenzo-18-crown-6 (DB18C6) and $DB18C6/Li^+$ complex in different solvents (water, methanol, chloroform, and nitrobenzene) have been analyzed using radial distribution function (RDF), coordination number (CN), and orientation profiles, in order to identify the role of solvents on complexation of DB18C6 with Li^+ , using molecular dynamics (MD) simulations.

- 2411 **Theoretical study on the chemical mechanism of enoyl-CoA hydratase and the form of inhibitor binding**, Xiaobin Cui, Rongxing He, Qinlei Yang, Wei Shen, Ming Li [Southwest University]

Enoyl-CoA hydratase (ECH) catalyzes the second step in the vital β -oxidation pathway of fatty acid metabolism. This enzyme catalyzes the syn-addition of a water molecule across the double bond of 4-(N,N-dimethylamino) cinnamoyl-CoA (DAC-CoA). In this work, the reaction mechanisms of ECH were investigated using the density functional theory (DFT) methods.

- 2410 **Polarizability of neutral copper clusters**, Pablo Jaque [Universidad Andres Bello], Alejandro Toro-Labbé

Neutral copper clusters are characterized through their molecular structures, binding energy and electric dipole polarizability. It is shown that the mean and anisotropy of polarizability tensor are useful properties in the characterization and rationalization of reactivity and growth patterns in copper clusters.

- 2409 **Mechanism of the palladium-catalyzed hydrothiolation of alkynes to thioethers: a DFT study**, Xing-hui Zhang[Lanzhou University of Arts and Science], Zhi-yuan Geng, Ke-tai Wang, Shan-shan Li

The mechanisms of the palladium-catalyzed hydrothiolation of alkynes with thiols were investigated using density functional theory at the B3LYP/6-31G(d, p) (SDD for Pd) level.

- 2408 **Molecular modeling in dioxane methanol interaction**, Dipti Sharma, Sagarika Sahoo, Bijay K. Mishra[Sambalpur University]

Molecular interaction between dioxane and methanol involves certain polar and nonpolar bonding to form a one to one complex. Interatomic distances between hydrogen and oxygen within 3 Å have been considered as hydrogen bonding.

- 2407 **Structural basis of valmerins as dual inhibitors of GSK3 β /CDK5**, Xiaolong Li, Xiaowei Wang, Zibin Tian, Houling Zhao, Da Liang, Weisong Li, Yujin Qiu [Affiliated Hospital of Weifang Medical University], Shaoyong Lu

See Applications / Medicinal Chemistry and Drug Design.

- 2404 **Theoretical study of the hydrogen bonding and infrared spectroscopy in the cis-vacant polymorph of dioctahedral 2:1 phyllosilicates**, Elizabeth Escamilla-Roa [Instituto de Astrofísica de Andalucía (CSIC)], Alfonso Hernández-Laguna, C. Ignacio Sainz-Díaz

The spatial geometry and local environment of hydroxyl groups of the cis-vacant (cv) crystal polymorph of dioctahedral 2:1 phyllosilicates are studied by computational methods, doing especial emphasis on the hydrogen bonds and electrostatic interactions of the hydroxyl groups with the neighbor atoms.

- 2403 **A computational study of hydrogen bonds in intermolecular systems of high complexity: arachno-pentaborane(11)···Y with Y = O₂ and N₂**, Abedin Zabardasti, Hamid Goudarziafshar, Maryam Salehnassaj, Boaz G. Oliveira [Universidade Federal da Bahia]

The interactions of arachno-B₅H₁₁ with N₂ and O₂ were theoretically studied. In the B₅H₁₁···N₂ and B₅H₁₁···O₂ complexes, the terminal hydrogens of B₅H₁₁ work as electron donors whereas the bridge ones as electron acceptors.

- 2402 **Theoretical study on the influence of the Mg^{2+} and Al^{3+} octahedral cations on the vibrational spectra of the hydroxy groups of dioctahedral 2:1 phyllosilicate models** ,N. Hernández-Haro [Instituto Andaluz de Ciencias de la Tierra], J. Ortega-Castro, M. Pruneda, C. I. Sainz-Díaz, A. Hernández-Laguna

The effect on the vibrational spectrum of the hydroxy groups in dioctahedral 2:1 phyllosilicates of the isomorphous cation substitution of Mg^{2+} by Al^{3+} in the octahedral sheet was investigated at the DFT level. Ortho, meta and para Mg^{2+} configurational polymorphs were defined.

- 2401 **Labelling Herceptin with a novel oxaliplatin derivative: a computational approach towards the selective drug delivery** ,José P. Cerón-Carrasco [Universidad de Murcia], Javier Cerezo, Alberto Requena, José Zuñiga, Julia Contreras-García, Sonali Chavan, Miguel Manrubia-Cobo, Horacio Pérez-Sánchez

The clinical use of platinum(II)-based drugs has serious side effects due to the non-specific reactions with both malignant and normal cells. To circumvent such major drawback, novel metallodrugs might be combined with suitable carrier molecules, as antibodies, to ensure selective attacks on tumours while sparing healthy tissues.

- 2400 **Molecular dynamics comparison of E. coli WrbA apoprotein and holoprotein** ,David Reha[Academy of Sciences of the Czech Republic], Balasubramanian Harish, Dhiraj Sinha, Zdenek Kukacka, James McSally, Olga Ettrichova, Petr Novak, Jannette Carey, Rüdiger Ettrich

See Applications / Protein Dynamics.

- 2396 **Conformational analysis of glutamic acid: a density functional approach using implicit continuum solvent model** ,Başak Turan, Cenk Selçuki[Ege University]

See Applications / Protein Conformational Analysis.

- 2393 **Accurate calculation of the ionization energies of the chlorine lone pairs in 1,1,1-trifluoro-2-chloroethane (HCFC-133a)** ,Gessenildo Pereira Rodrigues, Juracy Régis Lucena Jr., Elizete Ventura, Silmar Andrade do Monte [Universidade Federal da Paraíba]

The vertical ionization energies of the chlorine lone pairs in HCFC-133a have been calculated at the SCF (via Koopmans' theorem and including orbital relaxation) and correlated (ROMP2, OVGF, and ROCCSD(T)) levels. Dunning aug-cc-pVXZ (X = D, T, and Q) basis sets were employed, and the ROMP2 and ROCCSD(T) results were extrapolated to the complete basis set (CBS) limit.

- 2392 **Alkyl substituent effect on density, viscosity and chemical behavior of 1-alkyl-3-methylimidazolium chloride** ,Lourdes del Olmo, Isabel Lage-Estebanez [Universidad Autónoma de Madrid], Rafael López, José M. García de la Vega

Molecular structure of the conformers of 1- C_n -3-methylimidazolium chloride ($n = 1$ to 4) ionic liquids has been explored and the relationships with density and viscosity have been studied using COSMO related methodologies.

- 2367 **Quantum dynamics study of $H + DBr$ and $D + HBr$ reaction** ,Ai Jie Zhang, JianFeng Jia, Hai Shun Wu [Shanxi Normal University], Guo Zhong He

Time-dependent quantum wave packet calculations have been performed for the H + DBr and D + HBr reaction using the recent diabatic potential energy surfaces. Reaction probabilities, integral cross sections, and rate constants are obtained.

- 2353 **The mechanism of Menshutkin reaction in gas and solvent phases from the perspective of reaction electronic flux**, Santanab Giri, Ricardo Inostroza-Rivera, Bárbara Herrera, Alvaro S. Núñez, Fernando Lund, Alejandro Toro-Labbé

The mechanism of Menshutkin reaction, $\text{NH}_3 + \text{CH}_3\text{Cl} = [\text{CH}_3\text{-NH}_3]^+ + \text{Cl}^-$, has been thoroughly studied in both gas and solvent (H_2O and cyclohexane) phase. It has been found that solvents favor the reaction, both thermodynamically and kinetically.

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About 105 Papers from more than 30 Journals are cited.

1 APPLICATIONS (114) Page 2

1.1 Small Molecules (11)

Water and Solvation	Page 2	QSAR	Page 4
Organic Solvents	Page 3	Carbon Nanoparticles	Page 5
Med. Chem. And Drug Design	Page 3		

1.2 Biopolymers (57)

Bioinformatics and Cheminformatics	Page 6	Ligand Binding	Page 13
Protein Secondary Structure	Page 7	Enzyme Catalysis	Page 15
Protein Structure Prediction	Page 8	Protein-Protein Interactions	Page 17
Comparative or Homology Modeling	Page 8	Membrane Proteins	Page 18
Protein Conformational Analysis	Page 9	Protein Folding	Page 20
Protein Structure Analysis	Page 10	Protein-Nucleic Acids	Page 20
Protein Dynamics	Page 10	Nucleic Acids	Page 21

1.3 Polymers

1.4 Surfaces, Catalysts and Material

2 METHODOLOGY (25) Page 22

QSAR	Page 22	QM & QM/MM	Page 24
Potentials and Parameters	Page 22	Comparative or Homology	Page 27
Molecular Dynamics	Page 23	Ligand Docking	Page 28

3 JOURNAL REVIEWS (5) Page 30

Journal of Molecular Graphics and Modeling, 54, November, 2014.
 Journal of Computational Chemistry, 35 (26), October, 2014.
 Journal of Computational Chemistry, 35 (27), October, 2014.
 Journal of Computational Chemistry, 35 (28), October, 2014.
 Journal of Molecular Modeling, 20 (10), October, 2014.

4 ADDRESSES OF PRINCIPAL AUTHORS Page 39

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1. APPLICATIONS

1.1. Small Molecules

Water and Solvation

Glucose-Promoted Localization Dynamics of Excess Electrons in Aqueous Glucose Solution Revealed by Ab Initio Molecular Dynamics Simulation

Jinxiang Liu, Robert I. Cukier, Yuxiang Bu [Shandong University], and Yuan Shang

J. Chem. Theor. and Comp., **10**, 4189–4197, 2014.

Ab initio molecular dynamics simulations reveal that an excess electron (EE) can be more efficiently localized as a cavity-shaped state in aqueous glucose solution (AGS) than in water. Compared with that (~1.5 ps) in water, the localization time is shortened by ~0.7–1.2 ps in three AGSs (0.56, 1.12, and 2.87 M). Although the radii of gyration of the solvated EEs are all close to 2.6 Å in the four solutions, the solvated EE cavities in the AGSs become more compact and can localize ~80% of an EE, which is considerably larger than that (~40–60% and occasionally ~80%) in water.

Direct Mixing of Atomistic Solutes and Coarse-Grained Water

Mario Orsi [Queen Mary University of London], Wei Ding, and Michail Palaiokostas

J. Chem. Theor. and Comp., **10**, 4684–4693, 2014.

We present a new dual-resolution approach for coupling atomistic and coarse-grained models in molecular dynamics simulations of hydrated systems. In particular, a coarse-grained point dipolar water model is used to solvate molecules represented with standard all-atom force fields. A unique characteristic of our methodology is that the mixing of resolutions is direct, meaning that no additional or ad hoc scaling factors, intermediate regions, or extra sites are required. To validate the methodology, we compute the hydration free energy of 14 atomistic small molecules (analogs of amino acid side chains) solvated by the coarse-grained water.



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Water and Solvation (Cont'd)

Molecular Simulation of Water and Hydration Effects in Different Environments: Challenges and Developments for DFTB Based Models

Puja Goyal, Hu-Jun Qian, Stephan Irle, Xiya Lu, Daniel Roston, Toshifumi Mori, Marcus Elstner, and Qiang Cui [University of Wisconsin—Madison]

J. Phys. Chem. B., **118**, 11007–11027, 2014.

We discuss the description of water and hydration effects that employs an approximate density functional theory, DFTB3, in either a full QM or QM/MM framework. The goal is to explore, with the current formulation of DFTB3, the performance of this method for treating water in different chemical environments, the magnitude and nature of changes required to improve its performance, and factors that dictate its applicability to reactions in the condensed phase in a QM/MM framework. A relatively minor change (on the scale of $k_B T$) in the O–H repulsive potential is observed to substantially improve the structural properties of bulk water under ambient conditions; modest improvements are also seen in dynamic properties of bulk water.

Organic Solvents

Replica-Exchange Molecular Dynamics Simulations of Cellulose Solvated in Water and in the Ionic Liquid 1-Butyl-3-Methylimidazolium Chloride

Barmak Mostofian, Xiaolin Cheng, and Jeremy C. Smith [Oak Ridge National Laboratory]

J. Phys. Chem. B., **118**, 11037–11049, 2014.

Ionic liquids have become a popular solvent for cellulose pretreatment in biorefineries due to their efficiency in dissolution and their reusability. Understanding the interactions between cations, anions, and cellulose is key to the development of better solvents and the improvement of pretreatment conditions. While previous studies described the interactions between ionic liquids and cellulose fibers, shedding light on the initial stages of the cellulose dissolution process, we study the end state of that process by exploring the structure and dynamics of a single cellulose decamer solvated in 1-butyl-3-methyl-imidazolium chloride (BmimCl) and in water using replica-exchange molecular dynamics.

Medicinal Chemistry and Drug Design

Importance of cytochromes in cyclization reactions: Quantum chemical study on a model reaction of proguanil to cycloguanil

Minhajul Arfeen, Dhilon S. Patel, Sheenu Abbat, Nikhil Taxak and Prasad V. Bharatam [National Institute of Pharmaceutical Education and Research (NIPER)]

J. Comp. Chem., **35**, 2047–2055, 2014.

Proguanil, an anti-malarial prodrug, undergoes cytochrome P450 catalyzed biotransformation to the pharmacologically active triazine metabolite (cycloguanil), which inhibits plasmodial dihydrofolate reductase. This cyclization is catalyzed by CYP2C19 and many anti-malarial lead compounds are being designed and synthesized to exploit this pathway. Quantum chemical calculations were performed using the model species (Cpd I for active species of cytochrome and N4-isopropyl-N6-methylbiguanide for proguanil) to elucidate the mechanism of the cyclization pathway. The overall reaction involves the loss of a water molecule, and is exothermic by approximately 55 kcal/mol, and involves a barrier of approximately 17 kcal/mol.

Medicinal Chemistry and Drug Design (Cont'd)

Curation and Analysis of Multitargeting Agents for Polypharmacological Modeling

A. Srinivas Reddy, Zhi Tan, and Shuxing Zhang [University of Texas MD Anderson Cancer Center]

J.Chem. Infor. and Mod. **54**, 2536–2543, 2014.

In drug discovery and development, the conventional “single drug, single target” concept has been shifted to “single drug, multiple targets” – a concept coined as polypharmacology. For studies in this emerging field, dedicated and high-quality databases of multitargeting ligands would be exceedingly beneficial. To this end, we conducted a comprehensive analysis of the structural and chemical/biological profiles of polypharmacological agents and present a Web-based database (Polypharma). All of these compounds curated herein have been cocrystallized with more than one unique protein with intensive reports of their multitargeting activities.

Molecular Simulation of the Concentration-Dependent Interaction of Hydrophobic Drugs with Model Cellular Membranes

Myungshim Kang and Sharon M. Loverde [The City University of New York]
sharon.loverde@csi.cuny.edu

J. Phys. Chem. B., **118**, 11965–11972, 2014.

We report here the interactions between a hydrophobic drug and a model cellular membrane at the molecular level using all-atom molecular dynamics simulations of paclitaxel, a hydrophobic cancer drug. The calculated free energy of a single drug across the bilayer interface displays a minimum in the outer hydrophobic zone of the membrane. The transfer free energy shows excellent agreement with reported experimental data. In two sets of long-time simulations of high concentrations of drug in the membrane (12 and 11 mol %), the drugs display substantial clustering and rotation with significant directional preference in their diffusion.

Quantitative Structure-Activity Relations

Determinants of Activity at Human Toll-like Receptors 7 and 8: Quantitative Structure–Activity Relationship (QSAR) of Diverse Heterocyclic Scaffolds

Euna Yoo, Deepak B. Salunke, Diptesh Sil, Xiaoqiang Guo, Alex C. D. Salyer, Alec R. Hermanson, Manoj Kumar, Subbalakshmi S. Malladi, Rajalakshmi Balakrishna, Ward H. Thompson, Hiromi Tanji, Umeharu Ohto, Toshiyuki Shimizu, and Sunil A. David [University of Kansas]

J.Med.Chem., **57**, 7955–7970, 2014.

Toll-like receptor (TLR) 7 and 8 agonists are potential vaccine adjuvants, since they directly activate APCs and enhance Th1-driven immune responses. Previous SAR investigations in several scaffolds of small molecule TLR7/8 activators pointed to the strict dependence of the selectivity for TLR7 vis-à-vis TLR8 on the electronic configurations of the heterocyclic systems, which we sought to examine quantitatively with the goal of developing “heuristics” to define structural requisites governing activity at TLR7 and/or TLR8. We undertook a scaffold-hopping approach, entailing the syntheses and biological evaluations of 13 different chemotypes.

QSAR (Cont'd)

Modeling structure–activity relationships of prodiginines with antimalarial activity using GA/MLR and OPS/PLS

Luana Janaína de Campos, Eduardo Borges de Melo [Western Paraná State University (UNIOESTE)]

J. Mol.Graph. and Mod., **54**, 19-31 , 2014.

In the present study, we performed a multivariate quantitative structure-activity relationship (QSAR) analysis of 52 prodiginines with antimalarial activity. Variable selection was based on the genetic algorithm (GA) and ordered predictor selection (OPS) approaches, and the models were built using the multiple linear regression (MLR) and partial least squares (PLS) regression methods. The leave-N-out crossvalidation and y-randomization tests showed that the models were robust and free from chance correlation. The mechanistic interpretation of the results was supported by earlier findings.

Antioxidant activity of flavonoids: a QSAR modeling using Fukui indices descriptors

Houria Djeradi [University of Bechar], Ali Rahmouni, Abdelkrim Cheriti

J. Mol.Mod., **20**, 2476, 2014.

A QSAR model to predict the antioxidant activity of flavonoid compounds was developed. New electronic structure descriptors which are Fukui indices are correlated to the radical scavenging of flavonoids. These indices are obtained at DFT/B3LYP level of chemical quantum theory. The logIC₅₀ experimental values of antioxidant activity are taken from the literature. The model is based on the multilinear regression method. Both experimental and calculated data of 36 flavonoids compounds were analyzed. A good correlation coefficient ($R^2 = 0.8159$) is obtained and the antioxidant activities of test compounds are well predicted.

Carbon Nanoparticles

Structural characteristics of liquid nitromethane at the nanoscale confinement in carbon nanotubes

Yingzhe Liu [Xi'an Modern Chemistry Research Institute], Weipeng Lai, Tao Yu, Zhongxue Ge, Ying Kang

J. Mol.Mod., **20**, 2459, 2014.

The stability of energetic materials confined in the carbon nanotubes can be improved at ambient pressure and room temperature, leading to potential energy storage and controlled energy release. However, the microscopic structure of confined energetic materials and the role played by the confinement size are still fragmentary. In this study, molecular dynamics simulations have been performed to explore the structural characteristics of liquid nitromethane (NM), one of the simplest energetic materials, confined in a series of armchair single-walled carbon nanotubes (SWNTs) changing from (5,5) to (16,16) at ambient conditions.

1.2. Biopolymers

Bioinformatics and Cheminformatics

PyWATER: a PyMOL plug-in to find conserved water molecules in proteins by clustering

Hitesh Patel, Björn A. Grüning, Stefan Günther [Albert-Ludwigs-University], and Irmgard Merfort

Bioinformatics. **30**, 2978-2980, 2014.

Conserved water molecules play a crucial role in protein structure, stabilization of secondary structure, protein activity, flexibility and ligand binding. Clustering of water molecules in superimposed protein structures, obtained by X-ray crystallography at high resolution, is an established method to identify consensus water molecules in all known protein structures of the same family. PyWATER is an easy-to-use PyMOL plug-in and identifies conserved water molecules in the protein structure of interest. PyWATER and a tutorial are available at <https://github.com/hiteshpatel379/PyWATER>. PyMOL is available at <http://www.pymol.org/> or <http://sourceforge.net/projects/pymol/>.

ChemStable: a web server for rule-embedded naïve Bayesian learning approach to predict compound stability

Zhihong Liu, Minghao Zheng, Xin Yan, Qiong Gu, Johann Gasteiger, Johan Tijhuis, Peter Maas, Jiabo Li, Jun Xu [Sun Yat-sen University]

J. Comp. Aided. Mol. Design, **28**, 941-950, 2014.

Predicting compound chemical stability is important because unstable compounds can lead to either false positive or to false negative conclusions in bioassays. Experimental data (COMDECOM) measured from DMSO/H₂O solutions stored at 50 °C for 105 days were used to predict stability by applying rule-embedded naïve Bayesian learning, based upon atom center fragment (ACF) features. To build the naïve Bayesian classifier, we derived ACF features from 9,746 compounds in the COMDECOM dataset.

Bigger data, collaborative tools and the future of predictive drug discovery

Sean Ekins [Collaborations in Chemistry, 5616 Hilltop Needmore Road], Alex M. Clark, S. Joshua Swamidass, Nadia Litterman, Antony J. Williams

J. Comp. Aided. Mol. Design, **28**, 997-1008, 2014.

Over the past decade we have seen a growth in the provision of chemistry data and cheminformatics tools as either free websites or software as a service commercial offerings. These have transformed how we find molecule-related data and use such tools in our research. We now discuss how information from some drug discovery datasets can be made more accessible and how privacy of data should not overwhelm the desire to share it at an appropriate time with collaborators. We also discuss additional software tools that could be made available and provide our thoughts on the future of predictive drug discovery in this age of big data.

Bioinformatics and Cheminformatics (Cont'd)

Generalized Workflow for Generating Highly Predictive in Silico Off-Target Activity Models

Lennart T. Anger, Antje Wolf, Klaus-Juergen Schleifer [BASF SE, Carl-Bosch-Strasse 38], Dieter Schrenk, and Sebastian G. Rohrer

J.Chem. Infor. and Mod. **54**, 2411–2422, 2014.

Chemical structure data and corresponding measured bioactivities of compounds are nowadays easily available from public and commercial databases. However, these databases contain heterogeneous data from different laboratories determined under different protocols and, in addition, sometimes even erroneous entries. In this study, we evaluated the use of data from bioactivity databases for the generation of high quality in silico models for off-target mediated toxicity as a decision support in early drug discovery and crop-protection research. We chose human acetylcholinesterase (hAChE) inhibition as an exemplary end point for our case study.

Increasing stability of antibody via antibody engineering: Stability engineering on an anti-hVEGF

Shuang Wang, Ming Liu, Dadi Zeng, Weiye Qiu, Pingping Ma, Yunzhou Yu, Hongyan Chang and Zhiwei Sun [Beijing Institute of Biotechnology, Beijing]

Proteins: Stru. Fun. & Bioinf., **82**, 2620–2630, 2014.

Antibody stability is very important for expression, activity, specificity, and storage. This knowledge of antibody structure has made it possible for a computer-aided molecule design to be used to optimize and increase stability. Many computational methods have been built based on knowledge or structure, however, a good integrated engineering system has yet to be developed that combines these. In the current study, we designed an integrated computer-aided engineering protocol, which included several successful methods.

Protein Secondary Structure

Crowdsourcing Yields a New Standard for Kinks in Protein Helices

Henry R. Wilman, Jean-Paul Ebejer, Jiye Shi, Charlotte M. Deane, and Bernhard Knapp [University of Oxford]

J.Chem. Infor. and Mod. **54**, 2585–2593, 2014.

Kinks are functionally important structural features found in the α -helices of proteins. Structurally, they are points at which a helix abruptly changes direction. Current kink definition and identification methods often disagree with one another. Here we describe a crowdsourcing approach to obtain a reliable gold standard set of kinks. Using an online interface, we collected more than 10 000 classifications of 300 helices into straight, curved, or kinked categories. We found that participants were better at discriminating between straight and not-straight helices than between kinked and curved helices.

Exploring the free energy landscape of a model β -hairpin peptide and its isoform

Chitra Narayanan [University Heights, Newark] and Cristiano L. Dias

Proteins: Stru. Fun. & Bioinf., **82**, 2394–2402, 2014.

Secondary structural transitions from α -helix to β -sheet conformations are observed in several misfolding diseases including Alzheimer's and Parkinson's. Determining factors contributing favorably to the formation of each of these secondary structures is therefore essential to better understand these disease states. β -hairpin peptides form basic components of anti-parallel β -sheets and are suitable model systems for characterizing the fundamental forces stabilizing β -sheets in fibrillar structures. In this study, we explore the free energy landscape of the model β -hairpin peptide GB1 and its E2 isoform that preferentially adopts α -helical conformations at ambient conditions.

Protein Structure Prediction

Predicting the structures of complexes between phosphoinositide 3-kinase (PI3K) and romidepsin-related compounds for the drug design of PI3K/histone deacetylase dual inhibitors using computational docking and the ligand-based drug design approach

Akifumi Oda [Kanazawa University, Kakuma-machi], Ken Saijo, Chikashi Ishioka, Koichi Narita, Tadashi Katoh, Yurie Watanabe, Shuichi Fukuyoshi, Ohgi Takahashi

J. Mol.Graph. and Mod., **54**, 46-53, 2014.

Predictions of the three-dimensional (3D) structures of the complexes between phosphoinositide 3-kinase (PI3K) and two inhibitors were conducted using computational docking and the ligand-based drug design approach. The obtained structures were refined by structural optimizations and molecular dynamics (MD) simulations. The ligands were located deep inside the ligand binding pocket of the p110 α subunit of PI3K, and the hydrogen bond formations and hydrophobic effects of the surrounding amino acids were predicted. Although rough structures were obtained for the PI3K-inhibitor complexes before the MD simulations, the refinement of the structures by these simulations clarified the hydrogen bonding patterns of the complexes.

Improved PEP-FOLD Approach for Peptide and Miniprotein Structure Prediction

Yimin Shen, Julien Maupetit, Philippe Derreumaux, and Pierre Tufféry [INSERM U973, MTi]

J. Chem. Theor. and Comp., **10**, 4745–4758, 2014.

Peptides and mini proteins have many biological and biomedical implications, which motivates the development of accurate methods, suitable for large-scale experiments, to predict their experimental or native conformations solely from sequences. In this study, we report PEP-FOLD2, an improved coarse grained approach for peptide de novo structure prediction and compare it with PEP-FOLD1 and the state-of-the-art Rosetta program. Using a benchmark of 56 structurally diverse peptides with 25–52 amino acids and a total of 600 simulations for each system, PEP-FOLD2 generates higher quality models than PEP-FOLD1, and PEP-FOLD2 and Rosetta generate near-native or native models for 95% and 88% of the targets, respectively.

Comparative or Homology Modeling

Modeling, Molecular Dynamics Simulation, and Mutation Validation for Structure of Cannabinoid Receptor 2 Based on Known Crystal Structures of GPCRs

Zhiwei Feng, Mohammed Hamed Alqarni, Peng Yang, Qin Tong, Ananda Chowdhury, Lirong Wang, and Xiang-Qun Xie [University of Pittsburgh]

J.Chem. Infor. and Mod. **54**, 2483–2499, 2014.

The cannabinoid receptor 2 (CB2) plays an important role in the immune system. Although a few of GPCRs crystallographic structures have been reported, it is still challenging to obtain functional transmembrane proteins and high resolution X-ray crystal structures, such as for the CB2 receptor. In the present work, we used 10 reported crystal structures of GPCRs which had high sequence identities with CB2 to construct homology-based comparative CB2 models. We applied these 10 models to perform a prescreen by using a training set consisting of 20 CB2 active compounds and 980 compounds randomly selected from the National Cancer Institute (NCI) database.

Comparative or Homology Modeling (Cont'd)

Computational design of protein antigens that interact with the CDR H3 loop of HIV broadly neutralizing antibody 2F5

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Proteins: Stru. Fun. & Bioinf., **82**, 2770–2782, 2014.

Rational design of proteins with novel binding specificities and increased affinity is one of the major goals of computational protein design. Epitope-scaffolds are a new class of antigens engineered by transplanting viral epitopes of predefined structure to protein scaffolds, or by building protein scaffolds around such epitopes. Epitope-scaffolds are of interest as vaccine components to attempt to elicit neutralizing antibodies targeting the specified epitope. In this study we developed a new computational protocol, MultiGraft Interface, that transplants epitopes but also designs additional scaffold features outside the epitope to enhance antibody-binding specificity and potentially influence the specificity of elicited antibodies.

Protein Confirmational Analysis

Microscopic Hydration Properties of the A β ₁₋₄₂ Peptide Monomer and the Globular Protein Ubiquitin: A Comparative Molecular Dynamics Study

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J. Phys. Chem. B., **118**, 11591–11604, 2014.

Atomistic molecular dynamics simulations of eight selected conformations of a disordered protein, amyloid beta (1–42) (A β), and a globular protein, ubiquitin (UBQ), have been carried out in aqueous media at 310 K. Detailed analyses were carried out to compare the microscopic properties of water molecules present in the hydration layers of these systems. It is noticed that irrespective of the conformational heterogeneity among the A β monomers, water molecules hydrating their surfaces exhibit relatively faster dynamics as compared to water molecules hydrating UBQ.

Structural dynamics of the monoamine transporter homolog LeuT from accelerated conformational sampling and channel analysis

James R. Thomas, Patrick C. Gedeon and Jeffry D. Madura [Duquesne University, Pittsburgh]

Proteins: Stru. Fun. & Bioinf., **82**, 2289–2302, 2014.

The bacterial leucine transporter LeuT retains significant secondary structure similarities to the human monoamine transporters (MAT) such as the dopamine and serotonin reuptake proteins. The primary method of computational study of the MATs has been through the use of the crystallized LeuT structure. Different conformations of LeuT can give insight into mechanistic details of the MAT family. A conformational sampling performed through accelerated molecular dynamics simulations testing different combinations of the leucine substrate and bound sodium ions revealed seven distinct conformational clusters.

Protein Structure Analysis

Probing the Disordered Domain of the Nuclear Pore Complex through Coarse-Grained Molecular Dynamics Simulations

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Biophysical Journal. **107**, 1393-1402, 2014.

The distribution of disordered proteins (FG-nups) that line the transport channel of the nuclear pore complex (NPC) is investigated by means of coarse-grained molecular dynamics simulations. A one-bead-per-amino-acid model is presented that accounts for the hydrophobic/hydrophilic and electrostatic interactions between different amino acids, polarity of the solvent, and screening of free ions. The results indicate that the interaction of the FG-nups forms a high-density, doughnut-like distribution inside the NPC, which is rich in FG-repeats.

Analysis of the structure and dynamics of human serum albumin

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J. Mol.Mod., **20**, 2450, 2014.

Human serum albumin (HSA) is a biologically relevant protein that binds a variety of drugs and other small molecules. No less than 50 structures are deposited in the RCSB Protein Data Bank (PDB). Based on these structures, we first performed a clustering analysis. Despite the diversity of ligands, only two well defined conformations are detected, with a deviation of 0.46 nm between the average structures of the two clusters, while deviations within each cluster are smaller than 0.08 nm. Those two conformations are representative of the apoprotein and the HSA-myristate complex already identified in previous literature.

Distribution of Neutral Lipids in the Lipid Droplet Core

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J. Phys. Chem. B., **118**, 11145–11151, 2014.

Cholesteryl esters (CEs) are a form of cholesterol (CHOL) storage in the living cells, as opposed to free CHOL. CEs are major constituents of low density lipoprotein particles. Therefore, CEs are implicated in provoking atherosclerosis. Arranged into cytoplasmic lipid droplets (LDs), CEs are stored intracellularly. They can also be transported extracellularly by means of lipoproteins. In this work, large-scale molecular dynamics (MD) simulations are used to characterize the molecular structure of LDs containing various fractions (10–50 mol %) of cholesteryl oleate (CO) with respect to triolein (TO) fraction.

Protein Dynamics

Illuminating the origins of spectral properties of green fluorescent proteins via proteochemometric and molecular modeling

Chanin Nantasenamat [Mahidol University, Bangkok], Saw Simeon, Wiwat Owasirikul, Napat Songtawee, Maris Lapins, Virapong Prachayasittikul and Jarl E. S. Wikberg

J. Comp. Chem., **35**, 1951–1966, 2014.

Green fluorescent protein (GFP) has immense utility in biomedical imaging owing to its autofluorescent nature. In efforts to broaden the spectral diversity of GFP. Understanding the origins of spectral properties of GFP could be achieved by means of investigating its structure–activity relationship. The first quantitative structure–property relationship study for modeling the spectral properties, particularly the excitation and emission maximas, of GFP was previously proposed by us some years ago in which quantum chemical descriptors were used for model development.

Protein Dynamics (Cont'd)

Effects of system net charge and electrostatic truncation on all-atom constant pH molecular dynamics

Wei Chen and Jana K. Shen [University of Maryland, Baltimore]

J. Comp. Chem., **35**, 1986–1996, 2014.

Constant pH molecular dynamics offers a means to rigorously study the effects of solution pH on dynamical processes. Here, we address two critical questions arising from the most recent developments of the all-atom continuous constant pH molecular dynamics (CpHMD) method: (1) What is the effect of spatial electrostatic truncation on the sampling of protonation states? (2) Is the enforcement of electrical neutrality necessary for constant pH simulations? We first examined how the generalized reaction field and force-shifting schemes modify the electrostatic forces on the titration coordinates.

Predicting backbone α angles and dihedrals from protein sequences by stacked sparse auto-encoder deep neural network

James Lyons, Abdollah Dehzangi, Rhys Heffernan, Alok Sharma, Kuldip Paliwal, Abdul Sattar, Yaoqi Zhou and Yuedong Yang [Griffith University]

J. Comp. Chem., **35**, 2040–2046, 2014.

Because a nearly constant distance between two neighbouring α atoms, local backbone structure of proteins can be represented accurately by the angle between $\alpha_{i-1}-\alpha_i-\alpha_{i+1}$ (θ) and a dihedral angle rotated about the $\alpha_i-\alpha_{i+1}$ bond (τ). θ and τ angles, as the representative of structural properties of three to four amino-acid residues, offer a description of backbone conformations that is complementary to ϕ and ψ angles (single residue) and secondary structures (>3 residues). Here, we report the first machine-learning technique for sequence-based prediction of θ and τ angles. Predicted angles based on an independent test have a mean absolute error of 9° for θ and 34° for τ with a distribution on the θ - τ plane close to that of native values.

Effects of protein flexibility on the site of metabolism prediction for CYP2A6 substrates

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J. Mol. Graph. and Mod., **54**, 90-99, 2014.

Structure-based prediction for the site of metabolism (SOM) of a compound metabolized by human cytochrome P450s (CYPs) is highly beneficial in drug discovery and development. However, the flexibility of the CYPs' active site remains a huge challenge for accurate SOM prediction. Compared with other CYPs, the active site of CYP2A6 is relatively small and rigid. To address the impact of the flexibility of CYP2A6 active site residues on the SOM prediction for substrates, in this work, molecular dynamics (MD) simulations and molecular docking were used to predict the SOM of 96 CYP2A6 substrates.

Effects of Temperature on the Properties of Glycerol: A Computer Simulation Study of Five Different Force Fields

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J. Phys. Chem. B., **118**, 11284–11294, 2014.

[A!](#)

We perform MD simulations of glycerol (propane-1,2,3-triol) at normal pressure and a wide range of temperatures (300–460 K) and study the sensitivity of simulation results to the force field (FF) considered. We employ five commonly used FFs: (i) AMBER, (ii) CHARMM22, and (iii) three versions of the OPLS-AA FF (OPLS1, OPLS2, and OPLS3). We study thermodynamic (density $\rho(T)$, thermal expansion coefficient $\alpha_p(T)$, isobaric specific heat $c_p(T)$), dynamic (diffusion coefficient $D(T)$), as well as structural properties (molecular conformations and hydrogen-bond statistics).

Protein Dynamics (Cont'd)

Dimerization Process of Amyloid- β (29–42) Studied by the Hamiltonian Replica-Permutation Molecular Dynamics Simulations

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J. Phys. Chem. B., **118**, 11428–11436, 2014.

The amyloid- β peptides form amyloid fibrils which are associated with Alzheimer's disease. Amyloid- β (29–42) is its C-terminal fragment and a critical determinant of the amyloid formation rate. This fragment forms the amyloid fibril by itself. However, the fragment conformation in the fibril has yet to be determined. In order to investigate the dimerization process and conformations, we applied the Hamiltonian replica-permutation method, which is a better alternative to the Hamiltonian replica-exchange method, to two amyloid- β (29–42) molecules in explicit water solvent.

Local Water Dynamics around Antifreeze Protein Residues in the Presence of Osmolytes: The Importance of Hydroxyl and Disaccharide Groups

Anand Narayanan Krishnamoorthy, Christian Holm, and Jens Smiatek [Universität Stuttgart]

J. Phys. Chem. B., **118**, 11613–11621, 2014.

Antifreeze proteins (AFP) and antifreeze glycoproteins (AFGP) are synthesized by various organisms to enable their cells to survive low temperature environments like in the polar regions. The aim of this work is to examine the dynamics of water molecules around different antifreeze protein residues by using atomistic molecular dynamics simulations. A prototype of AFP from antarctic notothenioids with the main subunit alanine-alanine-threonine (AAT) and a mutant (polyalanine) together with the residues of an antifreeze glycoprotein (AFGP) were simulated and compared with respect to their influence on the local water shell.

Burial of nonpolar surface area and thermodynamic stabilization of globins as a function of chain elongation

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Proteins: Stru. Fun. & Bioinf., **82**, 2318–2331, 2014.

Proteins are biosynthesized from N to C terminus before they depart from the ribosome and reach their bioactive state in the cell. At present, very little is known about the evolution of conformation and the free energy of the nascent protein with chain elongation. These parameters critically affect the extent of folding during ribosome-assisted biosynthesis. Here, we address the impact of vectorial amino acid addition on the burial of nonpolar surface area and on the free energy of native-like structure formation in the absence of the ribosomal machinery.

Glucose oxidase from *Penicillium amagasakiense*: Characterization of the transition state of its denaturation from molecular dynamics simulations

Guido Todde, Sven Hovmöller, Aatto Laaksonen and Francesca Mocci [Stockholm University, Stockholm]

Proteins: Stru. Fun. & Bioinf., **82**, 2353–2363, 2014.

Glucose oxidase (GOx) is a flavoenzyme having applications in food and medical industries. However, GOx, as many other enzymes when extracted from the cells, has relatively short operational lifetimes. Several recent studies (both experimental and theoretical), carried out on small proteins, show that a detailed knowledge of how the breakdown process starts and proceeds on molecular level could be of significant help to artificially improve the stability of fragile proteins. We have performed extended MD simulations to study the denaturation of GOx to identify weak points in its structure and in this way gather information to later make it more stable, for example, by mutations.

Protein Dynamics (Cont'd)

Exploring the early stages of the pH-induced conformational change of influenza hemagglutinin

Yu Zhou, Chao Wu, Lifeng Zhao and Niu Huang [Beijing Normal University, Beijing]

Proteins: Stru. Fun. & Bioinf., **82**, 2412–2428, 2014.

Hemagglutinin (HA) mediates the membrane fusion process of influenza virus through its pH-induced conformational change. However, it remains challenging to study its structure reorganization pathways in atomic details. Here, we first applied continuous constant pH molecular dynamics approach to predict the pK_a values of titratable residues in H2 subtype HA. The calculated net-charges in HA1 globular heads increase from 0e (pH 7.5) to +14e (pH 4.5), indicating that the charge repulsion drives the detrimerization of HA globular domains.

De novo inference of protein function from coarse-grained dynamics

Pratiti Bhadra and Debnath Pal [Indian Institute of Science, Bangalore]

Proteins: Stru. Fun. & Bioinf., **82**, 2443–2454, 2014.

Inference of molecular function of proteins is the fundamental task in the quest for understanding cellular processes. The task is getting increasingly difficult with thousands of new proteins discovered each day. The difficulty arises primarily due to lack of high-throughput experimental technique for assessing protein molecular function, a lacunae that computational approaches are trying hard to fill. The latter too faces a major bottleneck in absence of clear evidence based on evolutionary information. We propose a de novo approach to annotate protein molecular function through structural dynamics match for a pair of segments from two dissimilar proteins, which may share even <10% sequence identity.

Structure-based simulations reveal concerted dynamics of GPCR activation

Nicholas Leioatts, Pooja Suresh, Tod D. Romo and Alan Grossfield [University of Rochester Medical Center]

Proteins: Stru. Fun. & Bioinf., **82**, 2538–2551, 2014.

G protein-coupled receptors (GPCRs) are a vital class of proteins that transduce biological signals across the cell membrane. However, their allosteric activation mechanism is not fully understood; crystal structures of active and inactive receptors have been reported, but the functional pathway between these two states remains elusive. Here, we use structure-based (Gō-like) models to simulate activation of two GPCRs, rhodopsin and the β_2 adrenergic receptor (β_2AR).

Ligand Binding/Docking

Molecular recognition pattern of cytotoxic alkaloid vinblastine with multiple targets

Prateek Pandya, Lokesh Kr Agarwal, Neelima Gupta, Sourav Pal [CSIR-National Chemical Laboratory]

J. Mol.Graph. and Mod., **54**, 1-9, 2014.

Vinblastine (VLB), a cytotoxic alkaloid is used extensively against various cancer types and the crystal structure of its tubulin complex is already known. Multitarget affinity of vinblastine has been investigated and the nature of binding with biological receptors namely, duplex DNA and Human serum albumin (HSA) has been compared to the binding characteristics of its known complex with natural high affinity receptor tubulin using molecular docking and QM-MM calculations. VLB is found to interact with DNA as well as HSA protein, though, with weaker affinity as compared to tubulin.

Ligand Binding / Docking (Cont'd)

Ab initio molecular simulations for proposing potent inhibitors to butyrylcholinesterases

Takeru Murakawa, Yuki Matsushita, Tomoya Suzuki, Mahmud Tareq Hassan Khan, Noriyuki Kurita [Toyohashi University of Technology]

J. Mol. Graph. and Mod., **54**, 54-61, 2014.

Butyrylcholinesterase (BChE) exists mainly at neuromuscular junctions and plays an important role in the hydrolyzing mechanism of neurotransmitter acetylcholine. A variety of compounds have been produced in order to inhibit the function of BChE. We here investigate the specific interactions between BChE and some ligands (Kx) with large binding affinity to BChE, using ligand-docking, classical molecular mechanics and ab initio fragment molecular orbital (FMO) methods. The binding energies between BChE and Kx evaluated by the FMO method have a correlation with the 50% inhibition concentration obtained by the previous experiments.

Theoretical study of polaron binding energy in conformationally disrupted oligosilanes

Barbora Hanulíková [University Institute, Nad Ovcírnou 3685], Ivo Kuritka

J. Mol. Mod., **20**, 2442, 2014.

Density functional theory was used for a quantum chemical study of oligo[methyl(phenyl)silylene] structures containing a conformational defect: a kink in the silicon backbone. Oligomers were studied in the neutral state as well as in the form of positive (P^+) and negative (P^-) polaron quasiparticles. Computations performed using the B3LYP model and the 6-31G(d) basis set revealed that the charge distribution is not influenced by the presence of the kink, but the positive charge on the Si backbone differs slightly in P^+ and P^- quasiparticles.

Molecular insight into γ - γ tubulin lateral interactions within the γ -tubulin ring complex (γ -TuRC)

Charu Suri, Triscia W. Hendrickson, Harish C. Joshi, Pradeep Kumar Naik [Jaypee University of Information Technology]

J. Comp. Aided. Mol. Design, **28**, 961-972, 2014.

γ -tubulin is essential for the nucleation and organization of mitotic microtubules in dividing cells. It is localized at the microtubule organizing centers and mitotic spindle fibres. The most well accepted hypothesis for the initiation of microtubule polymerization is that α/β -tubulin dimers add onto a γ -tubulin ring complex (γ TuRC), in which adjacent γ -tubulin subunits bind to the underlying non-tubulin components of the γ TuRC. This template thus determines the resulting microtubule lattice. In this study we use molecular modelling and molecular dynamics simulations, combined with computational MM-PBSA/MM-GBSA methods, to determine the extent of the lateral atomic interaction between two adjacent γ -tubulins within the γ TuRC.

Insights into a highly conserved network of hydrogen bonds in the agonist binding site of nicotinic acetylcholine receptors: A structural and theoretical study

Alexandre Atkinson, Jérôme Graton [Université de Nantes] and Jean-Yves Le Questel

Proteins: Stru. Fun. & Bioinf., **82**, 2303–2317, 2014.

Structural and theoretical studies on the geometrical features of a hydrogen-bond network occurring in the binding site of nicotinic acetylcholine receptors (nAChRs) and composed of interconnected WxPD (Trp-x-Pro-Asp) and SWyz (Ser-Trp-yz) sequences from loops A and B, respectively, have been carried out. Multiple sequence alignments using as template the sequence of the apoform of *Aplysia californica* acetylcholine binding protein (Ac-AChBP) show the strict conservation of serine and tryptophan residues of the loop B SWyz sequence.

Ligand Binding / Docking (Cont'd)

Molecular simulations of β -lactoglobulin complexed with fatty acids reveal the structural basis of ligand affinity to internal and possible external binding sites

Stefania Evoli, Rita Guzzi and Bruno Rizzuti [University of Calabria, Rende (CS)]

Proteins: Stru. Fun. & Bioinf., **82**, 2609–2619, 2014.

The interaction of saturated fatty acids of different length (C8:0 to C18:0) with β -lactoglobulin (β LG) was investigated by molecular dynamics simulation and docking approaches. The results show that the presence of such ligands in the hydrophobic central cavity of β LG, known as the protein calyx, determines an enhancement of atomic fluctuations compared with the unliganded form, especially for loops at the entrance of the binding site. Concerted motions are evidenced for protein regions that could favor the binding of ligands.

The recognition of membrane-bound PtdIns3P by PX domains

ZhiGuang Jia, Rajesh Ghai, Brett M. Collins and Alan E. Mark [The University of Queensland]

Proteins: Stru. Fun. & Bioinf., **82**, 2332–2342, 2014.

Phox-homology (PX) domains target proteins to the organelles of the secretory and endocytic systems by binding to phosphatidylinositol phospholipids (PIPs). Among all the structures of PX domains that have been solved, only three have been solved in a complex with the main physiological ligand: PtdIns3P. In this work, molecular dynamic simulations have been used to explore the structure and dynamics of the p40^{phox}-PX domain and the SNX17-PX domain and their interaction with membrane-bound PtdIns3P. In the simulations, both PX domains associated spontaneously with the membrane-bound PtdIns3P and formed stable complexes.

Molecular dynamics simulations of the auxin-binding protein 1 in complex with indole-3-acetic acid and naphthalen-1-acetic acid

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Proteins: Stru. Fun. & Bioinf., **82**, 2744–2755, 2014.

Auxin-binding protein 1 (ABP1) is suggested to be an auxin receptor which plays an important role in several processes in green plants. Maize ABP1 was simulated with the natural auxin indole-3-acetic acid (IAA) and the synthetic analog naphthalen-1-acetic acid (NAA), to elucidate the role of the KDEL sequence and the helix at the C-terminus. The KDEL sequence weakens the intermolecular interactions between the monomers but stabilizes the C-terminal helix. Conformational changes at the C-terminus occur within the KDEL sequence and are influenced by the binding of the simulated ligands.

Enzyme Catalysis

Role of Substrate Positioning in the Catalytic Reaction of 4-Hydroxyphenylpyruvate Dioxygenase—A QM/MM Study

Anna Wójcik, Ewa Broclawik, Per E. M. Siegbahn, Marcus Lundberg, Graham Moran, and Tomasz Borowski [Polish Academy of Sciences]

J. Am. Chem. Soc., 2013, **136**, 14472–14485, 2014.

Ring hydroxylation and coupled rearrangement reactions catalyzed by 4-hydroxyphenylpyruvate dioxygenase were studied with the QM/MM method ONIOM(B3LYP:AMBER). For electrophilic attack of the ferryl species on the aromatic ring, five channels were considered: attacks on the three ring atoms closest to the oxo ligand (C1, C2, C6) and insertion of oxygen across two bonds formed by them (C1–C2, C1–C6). For the subsequent migration of the carboxymethyl substituent, two possible directions were tested (C1→C2, C1→C6), and two different mechanisms were sought (stepwise radical, single-step heterolytic).

Enzyme Catalysis (Cont'd)

SAHA-based novel HDAC inhibitor design by core hopping method

Lan-Lan Zang, Xue-Jiao Wang, Xiao-Bo Li, Shu-Qing Wang, Wei-Ren Xu, Xian-Bin Xie, Xian-Chao Cheng, Huan Ma, Run-Ling Wang [Tianjin Medical University, Tianjin]

J. Mol.Graph. and Mod., **54**, 10-18, 2014.

The catalytic activity of the histone deacetylase (HDAC) is directly relevant to the pathogenesis of cancer, and HDAC inhibitors represented a promising strategy for cancer therapy. SAHA (suberoanilide hydroxamic acid), an effective HDAC inhibitor, is an anti-cancer agent against T-cell lymphoma. However, SAHA has adverse effects such as poor pharmacokinetic properties and severe toxicities in clinical use. In order to identify better HDAC inhibitors, a compound database was established by core hopping of SAHA, which was then docked into HDAC-8 (PDB ID: 1T69) active site to select a number of candidates with higher docking score and better interaction with catalytic zinc ion.

Catalytic Mechanism of L,D-Transpeptidase 2 from Mycobacterium tuberculosis Described by a Computational Approach: Insights for the Design of New Antibiotics Drugs

José Rogério A. Silva, Adrian E. Roitberg, and Cláudio Nahum Alves [Universidade Federal do Pará]

J.Chem. Infor. and Mod. **54**, 2402–2410, 2014.

Tuberculosis is perhaps the most persistent human disease caused by an infectious bacterium, *Mycobacterium tuberculosis*. The L,D-transpeptidase enzyme catalyzes the formation of 3 → 3 peptidoglycan cross-links of the Mtb cell wall and facilitates resistance against classical β -lactams. Herein, the experimentally proposed mechanism for Ldt_{Mt2} was studied by performing QM/MM MD simulations. The whole mechanistic process includes two stages: acylation and deacylation. During the acylation step, two steps were observed: the first step is a thiolate/imidazole ion-pair in the zwitterionic form, and the second step is the nucleophilic attack on the carboxyl carbon of the natural substrate accompanied by the breaking of the peptide bond on substrate.

Elucidating the Origin of the Esterase Activity of Human Serum Albumin Using QM/MM Calculations

Oraphan Phuangsawai, Supa Hannongbua, and M. Paul Gleeson [Kasetsart University]

J. Phys. Chem. B., **118**, 11886–11894, 2014.

Human serum albumin (HSA) is a critical transport plasma protein accounting for ~60% of the total protein content in blood. Remarkably, this protein is also found to display esterase activity. In this study, we apply theoretical studies to elucidate the origin of the esterase-like activity arising from the Sudlow site I. Using MD and QM/MM calculations, we investigate which active site residues are involved in the reaction, and the precise mechanistic sequence of events. Our results suggest Lys199, His242, and Arg257 help give rise to the esterase activity and that the most catalytically efficient active site configuration requires that both Lys199 and Aspirin are in their neutral forms.

Enzyme Catalysis (Cont'd)

Temperature-accelerated molecular dynamics gives insights into globular conformations sampled in the free state of the AC catalytic domain

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Proteins: Stru. Fun. & Bioinf., **82**, 2483–2496, 2014.

The catalytic domain of the adenyl cyclase (AC) toxin from *Bordetella pertussis* is activated by interaction with calmodulin (CaM), resulting in cAMP overproduction in the infected cell. In the X-ray crystallographic structure of the complex between AC and the C terminal lobe of CaM, the toxin displays a markedly elongated shape. As for the structure of the isolated protein, experimental results support the hypothesis that more globular conformations are sampled, but information at atomic resolution is still lacking. Here, we use temperature-accelerated molecular dynamics (TAMD) simulations to generate putative all-atom models of globular conformations sampled by CaM-free AC.

Protein-Protein Interactions

Discovery of binding proteins for a protein target using protein–protein docking-based virtual screening

Changsheng Zhang, Bo Tang, Qian Wang and Luhua Lai [Peking University, Beijing]

Proteins: Stru. Fun. & Bioinf., **82**, 2472–2482, 2014.

Target structure-based virtual screening, which employs protein–small molecule docking to identify potential ligands, has been widely used in small-molecule drug discovery. In the present study, we used a protein–protein docking program to identify proteins that bind to a specific target protein. In the testing phase, an all-to-all protein–protein docking run on a large dataset was performed. The three-dimensional rigid docking program SDOCK was used to examine protein–protein docking on all protein pairs in the dataset.

A multiscale approach to predicting affinity changes in protein–protein interfaces

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Proteins: Stru. Fun. & Bioinf., **82**, 2681–2690, 2014.

Substitution mutations in protein–protein interfaces can have a substantial effect on binding, which has consequences in basic and applied biomedical research. ZEMu (Zone Equilibration of Mutants) flexibilizes only a small region around the site of mutation, then computes its dynamics under a physics-based force field. We validate with 1254 experimental mutants (with 1–15 simultaneous substitutions) in a wide variety of different protein environments (65 protein complexes), and obtain a significant improvement in the accuracy of predicted $\Delta\Delta G$.

Hot-spot analysis to dissect the functional protein–protein interface of a tRNA-modifying enzyme

Stephan Jakobi, Tran Xuan Phong Nguyen, François Debaene, Alexander Metz, Sarah Sanglier-Cianféroni, Klaus Reuter and Gerhard Klebe [Philipps-Universität Marburg]

Proteins: Stru. Fun. & Bioinf., **82**, 2713–2732, 2014.

Interference with protein–protein interactions of interfaces larger than 1500 Å² by small drug-like molecules is notoriously difficult, particularly if targeting homodimers. The tRNA modifying enzyme Tgt is only functionally active as a homodimer. The detailed understanding of the spatial location and stability contribution of the individual interaction hot-spot residues and the plasticity of motifs involved in the interface formation is a crucial prerequisite for the rational identification of drug-like inhibitors addressing the respective dimerization interface.

Membrane Proteins and Lipid Peptide Interactions

Acceleration of Lateral Equilibration in Mixed Lipid Bilayers Using Replica Exchange with Solute Tempering

Kun Huang , Angel E. García [Rensselaer Polytechnic Institute, Troy]

J. Chem. Theor. and Comp, **10**, 4264–4272, 2014.

The lateral heterogeneity of cellular membranes plays an important role in many biological functions such as signaling and regulating membrane proteins. This heterogeneity can result from preferential interactions between membrane components or interactions with membrane proteins. One major difficulty in MD simulations aimed at studying the membrane heterogeneity is that lipids diffuse slowly and collectively in bilayers, and therefore, it is difficult to reach equilibrium in lateral organization in bilayer mixtures. Here, we propose the use of the replica exchange with solute tempering (REST) approach to accelerate lateral relaxation in heterogeneous bilayers.

Solvent-Free, Highly Coarse-Grained Models for Charged Lipid Systems

Anand Srivastava and Gregory A. Voth [The University of Chicago]

J. Chem. Theor. and Comp, **10**, 4730–4744, 2014.

We present a methodology to develop coarse-grained lipid models such that electrostatic interactions between the coarse-grained sites can be derived accurately from an all-atom molecular dynamics trajectory and expressed as an effective pairwise electrostatic potential with appropriate screening functions. The reference nonbonded forces from the all-atom trajectory are decomposed into separate electrostatic and van der Waals (vdW) forces, based on the multiscale coarse-graining method. The coarse-grained electrostatic potential is assumed to be a general function of unknown variables and the final site–site interactions are obtained variationally, where the residual of the electrostatic forces from the assumed field is minimized.

Triptan partition in model membranes

Irene Wood, Mónica Pickholz [Universidad de Buenos Aires]

J. Mol.Mod., **20**, 2463, 2014.

In this work, we report a MD simulations of protonated triptans, sumatriptan and naratriptan, in a fully hydrated bilayer of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidyl-choline (POPC). The simulations were carried out at two concentrations for each drug. Our results show partition between the lipid head-water interphase and water phase for both triptans, with increasing access to the water phase with increasing concentrations. The triptans were stabilized at the interphase through different specific interactions with the POPC bilayer such as hydrogen bonds, salt bridges, and cation- π .

Structural Protein–Ligand Interaction Fingerprints (SPLIF) for Structure-Based Virtual Screening: Method and Benchmark Study

C. Da and D. Kireev [University of North Carolina at Chapel Hill]

J.Chem. Infor. and Mod. **54**, 2555–2561, 2014.

Accurate and affordable assessment of ligand–protein affinity for structure-based virtual screening (SB-VS) is a standing challenge. Hence, empirical postdocking filters making use of various types of structure–activity information may prove useful. Here, we introduce one such filter based upon three-dimensional structural protein–ligand interaction fingerprints (SPLIF). SPLIF permits quantitative assessment of whether a docking pose interacts with the protein target similarly to a known ligand and rescues active compounds penalized by poor initial docking scores.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

All-Atom Molecular Dynamics Simulation of a Photosystem I/Detergent Complex

Bradley J. Harris, Xiaolin Cheng, and Paul Frymier
[University of Tennessee, Knoxville]

J. Phys. Chem. B., **118**, 11633–11645, 2014.

All-atom molecular dynamics (MD) simulation was used to investigate the solution structure and dynamics of the photosynthetic pigment–protein complex photosystem I (PSI) from *Thermosynechococcus elongatus* embedded in a toroidal belt of n-dodecyl- β -d-maltoside (DDM) detergent. Evaluation of root-mean-square deviations (RMSDs) relative to the known crystal structure show that the protein complex surrounded by DDM molecules is stable during the 200 ns simulation time, and root-mean-square fluctuation (RMSF) analysis indicates that regions of high local mobility correspond to solvent-exposed regions such as turns in the transmembrane α -helices and flexible loops on the stromal and luminal faces.

Molecular Dynamics Simulations of DPPC/CTAB Monolayers at the Air/Water Interface

Bin Liu, Matthew I. Hoopes, and Mikko Karttunen
[University of Waterloo]

J. Phys. Chem. B., **118**, 11723–11737, 2014.

An atomistic-level understanding of cationic lipid monolayers is essential for development of gene delivery agents based on cationic micelle-like structures. We employ molecular dynamics (MD) simulations for a detailed atomistic study of lipid monolayers composed of both pure zwitterionic dipalmitoylphosphatidylcholine (DPPC) and a mixture of DPPC and cationic cetyltrimethylammonium bromide (CTAB) at the air/water interface. We aim to investigate how the composition of the DPPC/CTAB monolayers affects their structural and electrostatic properties in the liquid-expanded phase.

Reconciling Structural and Thermodynamic Predictions Using All-Atom and Coarse-Grain Force Fields: The Case of Charged Oligo-Arginine Translocation into DMPC Bilayers

Yuan Hu, Sudipta Kumar Sinha, and Sandeep Patel
[University of Delaware, Newark]

J. Phys. Chem. B., **118**, 11973–11992, 2014.

Using the translocation of short, charged cationic oligo-arginine peptides (mono-, di-, and triarginine) from bulk aqueous solution into model DMPC bilayers, we explore the question of the similarity of thermodynamic and structural predictions obtained from molecular dynamics simulations using all-atom and Martini coarse-grain force fields. Specifically, we estimate potentials of mean force associated with translocation using standard all-atom (CHARMM36 lipid) and polarizable and nonpolarizable Martini force fields, as well as a series of modified Martini-based parameter sets. We find that we are able to reproduce qualitative features of potentials of mean force of single amino acid side chain analogues into model bilayers.

Protein Folding

Folding Simulations for Proteins with Diverse Topologies Are Accessible in Days with a Physics-Based Force Field and Implicit Solvent

Hai Nguyen, James Maier, He Huang, Victoria Perrone, and Carlos Simmerling [Stony Brook University]

J. Am. Chem. Soc., 2013, **136**, 13959–13962, 2014.

The millisecond time scale needed for molecular dynamics simulations to approach the quantitative study of protein folding is not yet routine. One approach to extend the simulation time scale is to perform long simulations on specialized and expensive supercomputers such as Anton. Approaches to this problem typically involve varied compromises between accuracy, precision, and cost; the goal here is to address whether simple implicit solvent models have become sufficiently accurate for their weaknesses to be offset by their ability to rapidly provide much more precise conformational data as compared to explicit solvent. We demonstrate that our recently developed physics-based model performs well on this challenge, enabling accurate all-atom simulated folding for 16 of 17 proteins with a variety of sizes, secondary structure, and topologies.

How the folding rates of two- and multistate proteins depend on the amino acid properties

Jitao T. Huang [Nankai University, Tianjin], Wei Huang, Shanran R. Huang and Xin Li

Proteins: Stru. Fun. & Bioinf., **82**, 2375–2382, 2014.

Proteins fold by either two-state or multistate kinetic mechanism. We observe that amino acids play different roles in different mechanism. Many residues that are easy to form regular secondary structures (α helices, β sheets and turns) can promote the two-state folding reactions of small proteins. Most of hydrophilic residues can speed up the multistate folding reactions of large proteins. Folding rates of large proteins are equally responsive to the flexibility of partial amino acids.

Protein-Nucleic acid Interactions

Learning protein–DNA interaction landscapes by integrating experimental data through computational models

Jianling Zhong, Todd Wasson, and Alexander J. Hartemink [Duke University]

Bioinformatics. **30**, 2868–2874, 2014.

Transcriptional regulation is directly enacted by the interactions between DNA and many proteins, including transcription factors (TFs), nucleosomes and polymerases. A critical step in deciphering transcriptional regulation is to infer, and eventually predict, the precise locations of these interactions, along with their strength and frequency. We develop a novel statistical framework that integrates different sources of experimental information within a thermodynamic model of competitive binding to jointly learn a holistic view of the *in vivo* protein–DNA interaction landscape.

Protein-Nucleic Acid Interactions (Cont'd)

Sensing Conformational Changes in DNA upon Ligand Binding Using QCM-D. Polyamine Condensation and Rad51 Extension of DNA Layers

Lu Sun, Karolin Frykholm, Louise H. Fornander, Sofia Svedhem, Fredrik Westerlund, and Björn Åkerman [Chalmers University of Technology]

J. Phys. Chem. B., **118**, 11895–11904, 2014.

Biosensors, in which binding of ligands is detected through changes in the optical or electrochemical properties of a DNA layer confined to the sensor surface, are important tools for investigating DNA interactions. Here, we investigate if conformational changes induced in surface-attached DNA molecules upon ligand binding can be monitored by the quartz crystal microbalance with dissipation (QCM-D) technique. DNA duplexes containing 59–184 base pairs were formed on QCM-D crystals by stepwise assembly of synthetic oligonucleotides of designed base sequences.

Nucleic Acids

Role of Microscopic Flexibility in Tightly Curved DNA

Maryna Taranova, Andrew D. Hirsh, Noel C. Perkins, and Ioan Andricioaei [University of California, Irvine]

J. Phys. Chem. B., **118**, 11028–11036, 2014.

The genetic material in living cells is organized into complex structures in which DNA is subjected to substantial contortions. Here we investigate the difference in structure, dynamics, and flexibility between two topological states of a short (107 base pair) DNA sequence in a linear form and a covalently closed, tightly curved circular DNA form. By employing a combination of all-atom molecular dynamics (MD) simulations and elastic rod modeling of DNA, which allows capturing microscopic details while monitoring the global dynamics, we demonstrate that in the highly curved regime the microscopic flexibility of the DNA drastically increases due to the local mobility of the duplex.

DNA Assisted Self-Assembly of PAMAM Dendrimers

Taraknath Mandal, Mattaparthi Venkata Satish Kumar, and Prabal K. Maiti [Indian Institute of Science, Bangalore]

J. Phys. Chem. B., **118**, 11805–11815, 2014.

We report DNA assisted self-assembly of polyamidoamine (PAMAM) dendrimers using all atom Molecular Dynamics (MD) simulations and present a molecular level picture of a DNA-linked PAMAM dendrimer nanocluster, which was first experimentally reported by Choi et al. (Nano Lett., **2004**, 4, 391–397). We have used single stranded DNA (ssDNA) to direct the self-assembly process. To explore the effect of pH on this mechanism, we have used both the protonated (low pH) and nonprotonated (high pH) dendrimers.

Local Structural and Environmental Factors Define the Efficiency of an RNA Pseudoknot Involved in Programmed Ribosomal Frameshift Process

Asmita Gupta and Manju Bansal [Indian Institute of Science, Bangalore]

J. Phys. Chem. B., **118**, 11905–11920, 2014.

In programmed –1 ribosomal frameshift, an RNA pseudoknot stalls the ribosome at specific sequence and restarts translation in a new reading frame. A precise understanding of structural characteristics of these pseudoknots and their PRF inducing ability has not been clear to date. To investigate this phenomenon, we have studied various structural aspects of a –1 PRF inducing RNA pseudoknot from BWYV using extensive molecular dynamics simulations. A set of functional and poorly functional forms, for which previous mutational data were available, were chosen for analysis.

Nucleic Acids (Cont'd)

The solution structure of full-length dodecameric MCM by SANS and molecular modeling

Susan Krueger [NIST Center for Neutron Research], Jae-Ho Shin, Joseph E. Curtis, Kenneth A. Robinson and Zvi Kelman

Proteins: Stru. Fun. & Bioinf., **82**, 2364–2374, 2014.

The solution structure of the full-length DNA helicase minichromosome maintenance protein from *Methanothermobacter thermautotrophicus* was determined by small-angle neutron scattering (SANS) data together with all-atom molecular modeling. The data were fit best with a dodecamer (dimer of hexamers). The 12 monomers were linked together by the B/C domains, and the adenosine triphosphatase (AAA+) catalytic regions were found to be freely movable in the full-length dodecamer both in the presence and absence of Mg^{2+} and 50-meric single-stranded DNA (ssDNA).

2. METHODOLOGY

Quantitative Structure-Activity Relations

Molecular Modeling of Exquisitely Selective c-Met Inhibitors through 3D-QSAR and Molecular Dynamics Simulations

Haoliang Yuan, Jin Zhuang, Shihe Hu, Huifang Li, Jinxing Xu, Yaning Hu, Xiao Xiong, Yadong Chen, and Tao Lu [China Pharmaceutical University]

J.Chem. Infor. and Mod. **54**, 2544–2554, 2014.

c-Met has been considered as an attractive target for developing antitumor agents. The highly selective c-Met inhibitors provide invaluable opportunities for the combination with other therapies safely to achieve the optimal efficacy. In this work, a series of triazolopyrazine c-Met inhibitors with exquisitely selectivity were investigated using a combination of molecular docking, three-dimensional quantitative structure–activity relationship (3D-QSAR), and molecular dynamics simulation. Comparative molecular field analysis (CoMFA) and comparative molecular similarity index analysis (CoMSIA) models were developed to reveal the structural determinants for c-Met inhibition.

Potentials and Parameters

ff14ipq: A Self-Consistent Force Field for Condensed-Phase Simulations of Proteins

David S. Cerutti, William C. Swope, Julia E. Rice, and David A. Case [BioMaPS Institute, Rutgers University]

J. Chem. Theor. and Comp., **10**, 4515–4534, 2014.

We present the ff14ipq force field, implementing the previously published IPolQ charge set for simulations of complete proteins. Minor modifications to the charge derivation scheme and van der Waals interactions between polar atoms are introduced. Torsion parameters are developed through a generational learning approach, based on gas-phase MP2/cc-pVTZ single-point energies computed of structures optimized by the force field itself rather than the quantum benchmark. In this manner, we sacrifice information about the true quantum minima in order to ensure that the force field maintains optimal agreement with the MP2/cc-pVTZ benchmark for the ensembles it will actually produce in simulations.

Potentials and Parameters (Cont'd)

AM1/d-CB1: A Semiempirical Model for QM/MM Simulations of Chemical Glycobiology Systems

Krishna Govender, Jiali Gao, and Kevin J. Naidoo [University of Cape Town]

J. Chem. Theor. and Comp., **10**, 4694–4707, 2014.

A semiempirical method based on the AM1/d Hamiltonian is introduced to model chemical glycobiological systems. We included in the parameter training set glycans and the chemical environment often found about them in glycoenzymes. Starting with RM1 and AM1/d-PhoT models we optimized H, C, N, O, and P atomic parameters targeting the best performing molecular properties that contribute to enzyme catalyzed glycan reaction mechanisms.

Molecular Dynamics

Computational Studies of the Effect of the S23D/S24D Troponin I Mutation on Cardiac Troponin Structural Dynamics

Yuanhua Cheng, Steffen Lindert, Peter Kekenes-Huskey, Vijay S. Rao, R. John Solaro, Paul R. Rosevear, Rommie Amaro, Andrew D. McCulloch, J. Andrew McCammon, Michaela Regnier [University of Washington]

Biophysical Journal. **107**, 1675–1685, 2014.

During β -adrenergic stimulation, cardiac troponin I (cTnI) is phosphorylated by protein kinase A (PKA) at sites S23/S24, located at the N-terminus of cTnI. This phosphorylation has been shown to decrease K_{Ca} and pCa_{50} , and weaken the cTnC-cTnI (C-I) interaction. In this study, we built up the cTn complex structure (including residues cTnC 1–161, cTnI 1–172, and cTnT 236–285) with the N-terminus of cTnI. We performed molecular-dynamics (MD) simulations to elucidate the structural basis of PKA phosphorylation-induced changes in cTn structure and Ca^{2+} binding.

Novel theoretically designed HIV-1 non-nucleoside reverse transcriptase inhibitors derived from nevirapine

Jinfeng Liu, Xiao He [East China Normal University], John Z. H. Zhang

J. Mol.Mod., **20**, 2451, 2014.

A common problem with non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV-1 is the emergence of mutations in the HIV-1 RT, in particular Lys103 $\rightarrow$ Asn (K103N) and Tyr181 $\rightarrow$ Cys (Y181C), which lead to resistance to this entire class of inhibitors. In this study, we theoretically designed two new non-nucleoside HIV-1 RT inhibitors, Mnev-1 and Mnev-2, derived from nevirapine, in order to reduce the resistance caused by those HIV-1 RT mutations. The binding modes of Mnev-1 and Mnev-2 with the wild-type HIV-1 RT and its mutants (K103N and Y181C) were suggested by molecular docking followed by 20-ns molecular dynamics (MD) simulations in explicit water of those binding complexes (HIV-1 RTs with the new inhibitors).

A Coupled Molecular Dynamics/Kinetic Monte Carlo Approach for Protonation Dynamics in Extended Systems

Gabriel Kabbe, Christoph Wehmeyer, and Daniel Sebastiani [Martin-Luther-University Halle-Wittenberg]

J. Chem. Theor. and Comp., **10**, 4221–4228, 2014.

We propose a multiscale simulation scheme that combines first-principles Molecular Dynamics (MD) and kinetic Monte Carlo (kMC) simulations to describe ion transport processes. On the one hand, the molecular dynamics trajectory provides an accurate atomistic structure and its temporal evolution, and on the other hand, the Monte Carlo part models the long-time motion of the acidic protons. Our hybrid approach defines a coupling scheme between the MD and kMC simulations that allows the kMC topology to adapt continuously to the propagating atomistic microstructure of the system.

Molecular Dynamics (Cont'd)

Dissipative Particle Dynamics with an Effective Pair Potential from Integral Equation Theory of Molecular Liquids

Alexander E. Kobryn, Dragan Nikolić, Olga Lyubimova, Sergey Gusarov, and Andriy Kovalenko [National Research Council of Canada]

J. Phys. Chem. B., **118**, 12034–12049, 2014.

We present a method of DPD simulation based on a coarse-grained effective pair potential obtained from the DRISM-KH molecular theory of solvation. The theory is first used to calculate the radial distribution functions of all-atom solute monomers in all-atom solvent and then to invert them into an effective pair potential between coarse-grained beads such that their fluid without solvent accounts for molecular specificities and solvation effects in the all-atom system. Bonded interactions are sampled in relatively short MD of the all-atom system and modeled with best multi-Gaussian fit. Replacing the heuristically defined conservative force potential in DPD, the coarse-grained effective pair potential is free from the artificial restrictions on potential range and shape and on equal volume of solute and solvent blobs inherent in standard DPD.

Specific potassium ion interactions facilitate homocysteine binding to betaine-homocysteine S-methyltransferase

Jana Mládková, Jana Hladílková, Carrie E. Diamond, Katherine Tryon, Kazuhiro Yamada, Timothy A. Garrow, Pavel Jungwirth, Markos Koutmos and Jiří Jiráček [Academy of Sciences of the Czech Republic]

Proteins: Stru. Fun. & Bioinf., **82**, 2552–2564, 2014.

Betaine-homocysteine S-methyltransferase (BHMT) is a zinc-dependent methyltransferase that uses betaine as the methyl donor for the remethylation of homocysteine to form methionine. This reaction supports S-adenosylmethionine biosynthesis, which is required for hundreds of methylation reactions in humans. Herein we report that BHMT is activated by potassium ions with an apparent K_M for K^+ of about 100 μM . The presence of potassium ions lowers the apparent K_M of the enzyme for homocysteine, but it does not affect the apparent K_M for betaine or the apparent k_{cat} for either substrate.

QM and QM/MM

Theory Uncovers an Unusual Mechanism of DNA Repair of a Lesioned Adenine by AlkB Enzymes

Binju Wang, Dandamudi Usharani, Chunsen Li, and Sason Shaik [Hebrew University of Jerusalem]

J. Am. Chem. Soc., 2013, **136**, 13895–13901, 2014.

DNA-base lesions cause cancer and propagate into the genome. We use in-protein QM/MM calculations to study the repair of etheno-bridged adenine (ϵA) by the iron(IV)-oxo species of AlkB enzymes. Recent experimental investigations, using mass-spectrometry and in crystallo isolation, suggested that ϵA was repaired by formation of an epoxide (ϵA -ep) that further transforms to a glycol (ϵA -gl), ending finally in adenine and glyoxal. Theory reproduces the experimentally observed barrier for the rate-determining step and its pH dependence.

QM and QM/MM (Cont'd)

On the electron affinity of cytosine in bulk water and at hydrophobic aqueous interfaces

Esteban Vöhringer-Martinez [Universität Leipzig], Ciro Dörner, Bernd Abel

J. Mol.Mod., **20**, 2453, 2014.

In the past one possible mechanism of DNA damage in bulk water has been attributed to the presence of hydrated electrons in water. Recently, one important property of hydrated electrons, namely their binding energy, was reported to be smaller at hydrophobic interfaces than in bulk aqueous solution. This possibly opens up new reaction possibilities with different solutes such as the DNA at hydrophobic, aqueous interfaces. Here, we use QM/MM molecular dynamics simulation to study how the molecular environment at the vacuum-water interface and in the bulk alters the electron affinity of cytosine being a characteristic part of the DNA.

A Novel, Computationally Efficient Multipolar Model Employing Distributed Charges for Molecular Dynamics Simulations

Mike Devereux, Shampa Raghunathan, Dmitri G. Fedorov, and Markus Meuwly [Universität Basel]

J. Chem. Theor. and Comp, **10**, 4229–4241, 2014.

A truncated multipole expansion can be re-expressed exactly using an appropriate arrangement of point charges. This means that groups of point charges that are shifted away from nuclear coordinates can be used to achieve accurate electrostatics for molecular systems. We introduce a multipolar electrostatic model formulated in this way for use in computationally efficient multipolar molecular dynamics simulations with well-defined forces and energy conservation in NVE (constant number–volume–energy) simulations.

Size-Consistent Multipartitioning QM/MM: A Stable and Efficient Adaptive QM/MM Method

Hiroshi C. Watanabe [Tokyo Institute of Technology], Tomáš Kubař, and Marcus Elstner

J. Chem. Theor. and Comp, **10**, 4242–4252, 2014.

We propose a new adaptive QM/MM method, the size-consistent multipartitioning (SCMP) QM/MM scheme, which enables stable and computationally efficient QM/MM simulations. A number of partitionings with identical size of the QM and the MM regions are considered with a new adaptive scheme in order to (1) realize smooth QM/MM switching, (2) introduce a conserved quantity (total energy, Hamiltonian), (3) avoid spurious artificial forces on the QM/MM border, and (4) allow for an efficient parallel implementation.

Free Energies of Quantum Particles: The Coupled-Perturbed Quantum Umbrella Sampling Method

William J. Glover, Jennifer R. Casey, and Benjamin J. Schwartz [University of California, Los Angeles]

J. Chem. Theor. and Comp, **10**, 4661–4671, 2014.

We introduce a new simulation method called Coupled-Perturbed Quantum Umbrella Sampling that extends the classical umbrella sampling approach to reaction coordinates involving quantum mechanical degrees of freedom. The central idea in our method is to solve coupled-perturbed equations to find the response of the quantum system's wave function along a reaction coordinate of interest. This allows for propagation of the system's dynamics under the influence of a quantum biasing umbrella potential and provides a method to rigorously undo the effects of the bias to compute equilibrium ensemble averages. In this way, one can drag electrons into regions of high free energy where they would otherwise not go, thus enabling chemistry by fiat.

QM and QM/MM (Cont'd)

Evaluating AM1/d-CB1 for Chemical Glycobiology QM/MM Simulations

Krishna K. Govender and Kevin J. Naidoo [University of Cape Town]

J. Chem. Theor. and Comp., **10**, 4708–4717, 2014.

The newly parametrized AM1/d-CB1 is evaluated for its performance in modeling monosaccharide structure, carbohydrate ring pucker, amino acid proton transfer, DNA base pair interactions, carbohydrate–aromatic π interactions, and phosphates that are prominent in glycosyltransferases. The accuracy of the method in these computations is compared to a comprehensive range of NDDO methods commonly used to study glycan structure and reactivity in chemical biology. AM1/d-CB1 shows significant improvement over existing NDDO type methods in the computation of five and six membered carbohydrate ring pucker free energy surfaces.

Experimental and Quantum Chemical Modeling Studies of the Interactions of L-Phenylalanine with Divalent Transition Metal Cations

Shilpi Mandal, Gunajyoti Das [North Eastern Hill University], and Hassan Askari

J. Chem. Infor. and Mod. **54**, 2524–2535, 2014.

Encoded by the UUU and UUC codons of the genetic code, L-phenylalanine (LPA) serves as an important precursor for tyrosine and various other compounds that are necessary to support life on earth. Here, we report the synthesis (both in solid and solvent phases) and characterization of the Ni^{2+} , Cu^{2+} , and Zn^{2+} complexes of LPA by several analytical, spectral, thermal, and electrochemical techniques. The results reveal that the products formed by following the two synthetic approaches are the same, and the metal ions bind to the LPA molecules in a 1:2 molar ratio (M^{+2}/LPA).

A Hybrid QM/MM Simulation Study of Intramolecular Proton Transfer in the Pyridoxal 5'-Phosphate in the Active Site of Transaminase: Influence of Active Site Interaction on Proton Transfer

Sindrila Dutta Banik and Amalendu Chandra [Indian Institute of Technology, Kanpur]

J. Phys. Chem. B., **118**, 11077–11089, 2014.

Pyridoxal 5'-phosphate (PLP) Schiff base, a versatile cofactor, exhibits a tautomeric equilibrium that involves an intramolecular proton transfer between the N-protonated zwitterionic ketoenamine tautomer and the O-protonated covalent enolimine tautomer. It has been postulated that for the catalytic activity, the PLP has to be in the zwitterionic ketoenamine tautomeric form. However, the exact position of the tautomeric equilibrium of Schiff base in the active site of PLP-dependent enzyme is not known yet. In the present work, we investigated the tautomeric equilibrium for the external aldimine state of PLP aspartate (PLP-Asp) Schiff base in the active site of aspartate aminotransferase (AspAT) using combined QM and molecular mechanical simulations.

QM and QM/MM (Cont'd)

Exciton Circular Dichroism in Channelrhodopsin

Gennaro Pescitelli, Hideaki E. Kato, Satomi Oishi, Jumpei Ito, Andrés Daniel Maturana, Osamu Nureki, and Robert W. Woody [Università di Pisa]

J. Phys. Chem. B., **118**, 11873–11885, 2014.

Channelrhodopsins (ChRs) are of great interest currently because of their important applications in optogenetics, the photostimulation of neurons. The absorption and circular dichroism (CD) spectra of C1C2, a chimera of ChR1 and ChR2 of *Chlamydomonas reinhardtii*, have been studied experimentally and theoretically. The visible absorption spectrum of C1C2 shows vibronic fine structure in the 470 nm band, consistent with the relatively nonpolar binding site. The CD spectrum has a negative band at 492 nm ($\Delta\epsilon_{\text{max}} = -6.17 \text{ M}^{-1} \text{ cm}^{-1}$) and a positive band at 434 nm ($\Delta\epsilon_{\text{max}} = +6.65 \text{ M}^{-1} \text{ cm}^{-1}$), indicating exciton coupling within the C1C2 dimer. Time-dependent density functional theory (TDDFT) calculations are reported for three models of the C1C2 chromophore.

Comparative or Homology Modeling

Molecular modeling and simulation of the human eNOS reductase domain, an enzyme involved in the release of vascular nitric oxide

N. T. Devika, Prakash Amresh, Md. Imtiyaz Hassan, B. M. Jaffar Ali [Jamia Millia Islamia]

J. Mol.Mod., **20**, 2470, 2014.

Homology modeling of the reductase domain of endothelial nitric oxide synthase (eNOS), which regulates the catalytic activity of eNOS, and molecular dynamics studies focusing especially on the serine residues S615, S633, and S1177 were performed. MD analysis of this structure revealed that S633 is highly flexible and accessible to solvent molecules, while S1177 becomes highly flexible when S633 is phosphorylated. The presence of intramolecular interactions between S1177 among the major serine residues underscores its structural importance to the efficient synthesis of nitric oxide in endothelium.

Structures of mesophilic and extremophilic citrate synthases reveal rigidity and flexibility for function

Stephen A. Wells [University of Bath, BATH], Susan J. Crennell and Michael J. Danson

Proteins: Stru. Fun. & Bioinf., **82**, 2657–2670, 2014.

Citrate synthase (CS) catalyses the entry of carbon into the citric acid cycle and is highly-conserved structurally across the tree of life. Crystal structures of dimeric CSs are known in both “open” and “closed” forms, which differ by a substantial domain motion that closes the substrate-binding clefts. We explore both the static rigidity and the dynamic flexibility of CS structures from mesophilic and extremophilic organisms from all three evolutionary domains. The computational expense of this wide-ranging exploration is kept to a minimum by the use of rigidity analysis and rapid all-atom simulations of flexible motion, combining geometric simulation and elastic network modeling.

Ligand Docking

A Gly-Zipper Motif Mediates Homodimerization of the Transmembrane Domain of the Mitochondrial Kinase ADCK3

Ambalika S. Khadria, Benjamin K. Mueller, Jonathan A. Stefely, Chin Huat Tan, David J. Pagliarini [University of Wisconsin-Madison], and Alessandro Senes

J. Am. Chem. Soc., 2013, **136**, 14068–14077, 2014.

Interactions between α -helices within the hydrophobic environment of lipid bilayers are integral to the folding and function of transmembrane proteins; however, the major forces that mediate these interactions remain debated, and our ability to predict these interactions is still largely untested. We recently demonstrated that the frequent transmembrane association motif GAS_{right}, the GxxxG-containing fold of the glycophorin A dimer, is optimal for the formation of extended networks of C α –H hydrogen bonds. Here, we demonstrate that this computational method can be used to characterize the structure of a protein not previously known to dimerize, by predicting and validating the transmembrane dimer of ADCK3, a mitochondrial kinase.

Combined docking, molecular dynamics simulations and spectroscopic studies for the rational design of a dipeptide ligand for affinity chromatography separation of human serum albumin

Elham Aghaee, Jahan B. Ghasemi [KN Toosi University of Technology], Firouzeh Manouchehri, Saeed Balalaie

J. Mol.Mod., **20**, 2446, 2014.

A computational approach to designing a peptide-based ligand for the purification of human serum albumin (HSA) was undertaken using molecular docking and molecular dynamics (MD) simulation. A three-step procedure was performed to design a specific ligand for HSA. Based on the candidate pocket structure of HSA (warfarin binding site), a peptide library was built. These peptides were then docked into the pocket of HSA using the GOLD program. The GOLDScore values were used to determine the affinity of peptides for HSA. Consequently, the dipeptide Trp–Trp, which shows a high GOLDScore value, was selected and linked to a spacer arm of Lys[CO(CH₂)₅NH] on the surface of ECH-lysine sepharose 4 gel.

An integrated approach to knowledge-driven structure-based virtual screening

Angela M. Henzler, Sascha Urbaczek, Matthias Hilbig, Matthias Rarey [University of Hamburg, Bundesstraße 43]

J. Comp. Aided. Mol. Design, **28**, 927-939, 2014.

In many practical applications of structure-based virtual screening (VS) ligands are already known. This circumstance requires that the obtained hits need to satisfy initial made expectations i.e., they have to fulfill a predefined binding pattern and/or lie within a predefined physico-chemical property range. Based on the Rapid Index-based Screening Engine (RAISE) approach, we introduce cRAISE—a user-controllable structure-based VS method. It efficiently realizes pharmacophore-guided protein-ligand docking to assess the library content but thereby concentrates only on molecules that have a chance to fulfill the given binding pattern.

Binding site multiplicity with fatty acid ligands: Implications for the regulation of PKR kinase autophosphorylation with palmitate

Liang Fang, Hyun Ju Cho, Christina Chan and Michael Feig [Michigan State University, East Lansing]

Proteins: Stru. Fun. & Bioinf., **82**, 2429–2442, 2014.

Saturated long chain-free fatty acids (FFAs), especially palmitate, have been implicated in apoptosis by inhibiting the activity of PKR (double-stranded RNA-dependent protein kinase). We recently found evidence that palmitate interacts directly with the kinase domain of PKR, subsequently inhibiting the autophosphorylation of PKR. To investigate the interactions of palmitate with PKR and its effects on PKR autophosphorylation, we performed extensive unbiased MD simulations combined with biochemical and biophysical experiments.

Ligand Docking (Cont'd)

A multiscale model for simulating binding kinetics of proteins with flexible linkers

Jiawen Chen, Zhong-Ru Xie and Yinghao Wu [Albert Einstein College of Medicine of Yeshiva University]

Proteins: Stru. Fun. & Bioinf., **82**, 2512–2522, 2014.

The kinetics of protein interactions are essential determinants in many cellular processes such as signal transduction and transcriptional regulation. Many proteins involved in these functions contain intrinsic disordered regions. This makes conformational flexibility become an unneglectable factor when studying the binding kinetic of these proteins. Using a small protein that contains two domains and a connecting loop as a testing system, we developed a multiscale simulation framework to study the role of flexible linkers in regulating kinetics of protein binding.

Computational identification of post-translational modification-based nuclear import regulations by characterizing nuclear localization signal-import receptor interaction

Jhih-Rong Lin, Zhonghao Liu and Jianjun Hu [University of South Carolina, Columbia]

Proteins: Stru. Fun. & Bioinf., **82**, 2783–2796, 2014.

The binding affinity between a nuclear localization signal (NLS) and its import receptor is closely related to corresponding nuclear import activity. PTM-based modulation of the NLS binding affinity to the import receptor is one of the most understood mechanisms to regulate nuclear import of proteins. However, identification of such regulation mechanisms is challenging due to the difficulty of assessing the impact of PTM on corresponding nuclear import activities. In this study we proposed NIpredict, an effective algorithm to predict nuclear import activity given its NLS.

3. JOURNAL REVIEWS

Journal of Molecular Graphics and Modelling, 54, November, 2014.

- 1-9 **Molecular recognition pattern of cytotoxic alkaloid vinblastine with multiple targets**, Prateek Pandya, Lokesh Kr Agarwal, Neelima Gupta, Sourav Pal [CSIR-National Chemical Laboratory]

See Applications / Ligand Binding.

- 10-18 **SAHA-based novel HDAC inhibitor design by core hopping method**, Lan-Lan Zang, Xue-Jiao Wang, Xiao-Bo Li, Shu-Qing Wang, Wei-Ren Xu, Xian-Bin Xie, Xian-Chao Cheng, Huan Ma, Run-Ling Wang [Tianjin Medical University, Tianjin]

See Applications / Enzyme Catalysis.

- 19-31 **Modeling structure–activity relationships of prodiginines with antimalarial activity using GA/MLR and OPS/PLS**, Luana Janaína de Campos, Eduardo Borges de Melo [Western Paraná State University (UNIOESTE)]

See Applications / QSAR.

- 32-45 **Theoretical prediction of maximum capacity of C₈₀ and Si₈₀ fullerenes for noble gas storage**, Zabiollah Mahdaviifar [Shahid Chamran University]

In this paper, we try to demonstrate that how many helium, neon and argon atoms can be trapped into fullerene cages until the pressure becomes large enough to break the C₈₀ and Si₈₀ frameworks. The maximum number of helium, neon and argon atoms which can be encapsulated into C₈₀ fullerene, is found with 46, 24 and 10 atoms respectively.

- 46-53 **Predicting the structures of complexes between phosphoinositide 3-kinase (PI3K) and romidepsin-related compounds for the drug design of PI3K/histone deacetylase dual inhibitors using computational docking and the ligand-based drug design approach**, Akifumi Oda [Kanazawa University, Kakuma-machi], Ken Saijo, Chikashi Ishioka, Koichi Narita, Tadashi Katoh, Yurie Watanabe, Shuichi Fukuyoshi, Ohgi Takahashi

See Applications / Protein Structure Prediction.

- 54-61 **Ab initio molecular simulations for proposing potent inhibitors to butyrylcholinesterases**, Takeru Murakawa, Yuki Matsushita, Tomoya Suzuki, Mahmud Tareq Hassan Khan, Noriyuki Kurita [Toyohashi University of Technology]

See Applications / Ligand Binding.

- 62-79 **Challenges in computational studies of enzyme structure, function and dynamics**, Alexandra T.P. Carvalho, Alexandre Barrozo, Dvir Doron, Alexandra Vardi Kilshtain, Dan Thomas Major, Shina Caroline Lynn Kamerlin [Uppsala University]

In this review we give an overview of the field of Computational enzymology. We start by describing the birth of the field, with emphasis on the work of the 2013 chemistry Nobel Laureates.

- 80-89 **Interactions of small gold clusters, Au_n ($n = 1-3$), with graphyne: Theoretical investigation**, Elmira Azizi, Zahra Aliakbar Tehrani, Zahra Jamshidi [Chemistry and Chemical Engineering Research Center of Iran]

The interactions of gold atom and clusters (Au_2 and Au_3) with the active sites of graphyne (GY) have been investigated using density functional theory (PBE, PBE-D3, and B3LYP-D3). In order to compare performance of DFT functional (BP86, PBE, TPSSh, B3LYP, PBE-D3, TPSSh-D3, and B3LYP-D3), the interactions of Au_2 with various functional groups such as sp , sp^2 and aromatic sp^2 carbon atoms, sp , sp^2 and aromatic sp^2 -bonds have been investigated and also compared with the ab initio MP2 results.

- 90-99 **Effects of protein flexibility on the site of metabolism prediction for CYP2A6 substrates**, Yayun Sheng, Yingjie Chen, Lei Wang, Guixia Liu, Weihua Li, Yun Tang [East China University of Science and Technology]

See Applications / Protein Dynamics.

Journal of Computational Chemistry, 35 (26), October, 2014.

- 1883–1889 **Hydrogen–hydrogen interaction in planar biphenyl: A theoretical study based on the interacting quantum atoms and Hirshfeld atomic energy partitioning methods**, Kiamars Eskandari [Isfahan University of Technology] and Christian Van Alsenoy

The nature of H-H interaction between ortho-hydrogen atoms in planar biphenyl is investigated by two different atomic energy partitioning methods, namely fractional occupation iterative Hirshfeld (FOHI) and interacting quantum atoms (IQA), and compared with the traditional virial-based approach of quantum theory of atoms in molecules (QTAIM).

- 1890–1899 **SurfKin: An ab initio kinetic code for modeling surface reactions**, Thong Nguyen-Minh Le, Bin Liu and Lam K. Huynh [Institute for Computational Science and Technology, Ho Chi Minh City]

In this article, we describe a C/C++ program called SurfKin (Surface Kinetics) to construct microkinetic mechanisms for modeling gas–surface reactions. Thermodynamic properties of reaction species are estimated based on density functional theory calculations and statistical mechanics.

- 1900–1915 **Calculating core-level excitations and x-ray absorption spectra of medium-sized closed-shell molecules with the algebraic-diagrammatic construction scheme for the polarization propagator**, Jan Wenzel, Michael Wormit and Andreas Dreuw [Ruprecht-Karls University]

Core-level excitations are generated by absorption of high-energy radiation such as X-rays. To describe these energetically high-lying excited states theoretically, we have implemented a variant of the algebraic-diagrammatic construction scheme of second-order ADC(2) by applying the core-valence separation (CVS) approximation to the ADC(2) working equations.

- 1916–1920 **Molecular sensing using armchair graphene nanoribbon**, Mohammad Reza Rezapour, Arunkumar Chitteth Rajan and Kwang S. Kim [Ulsan National Institute of Science and Technology (UNIST)]

In molecular electronics, the conductance strongly depends on the frontier energy levels and spatial orientations of molecules. Utilizing these features, we investigate the electron transport characteristics of conjugated molecules attached on an armchair graphene nanoribbon.

- 1921–1929 **Applicability of density functional theory in reproducing accurate vibrational spectra of surface bound species**, Ivana Matanović [University of New Mexico, Albuquerque], Plamen Atanasov, Boris Kiefer, Fernando H. Garzon and Neil J. Henson

The structural equilibrium parameters, the adsorption energies, and the vibrational frequencies of the nitrogen molecule and the hydrogen atom adsorbed on the (111) surface of rhodium have been investigated using different generalized-gradient approximation (GGA), nonlocal correlation, meta-GGA, and hybrid functionals, namely, Perdew, Burke, and Ernzerhof (PBE), Revised-RPBE, vdW-DF, Tao, Perdew, Staroverov, and Scuseria functional (TPSS), and Heyd, Scuseria, and Ernzerhof (HSE06) functional in the plane wave formalism.

Journal of Computational Chemistry, 35 (27), October, 2014.

- 1943–1950 **Insights into the influence of dispersion correction in the theoretical treatment of guanidine-quinoline copper(I) complexes**, Alexander Hoffmann, Richard Grunzke and Sonja Herres-Pawlis [Ludwig-Maximilians-Universität München]

For the description of steric effects, dispersion correction is important in density functional theory. By investigation of sterically encumbered guanidine-quinoline copper bis(chelate) complexes, we could show that the correct description requires modern dispersion correction using Becke–Johnson (BJ) damping and that earlier dispersion corrections are not sufficient.

- 1951–1966 **Illuminating the origins of spectral properties of green fluorescent proteins via proteochemometric and molecular modeling**, Chanin Nantasenamat [Mahidol University, Bangkok], Saw Simeon, Wiwat Owasirikul, Napat Songtawee, Maris Lapins, Virapong Prachayasittikul and Jarl E. S. Wikberg

See Applications / Protein Dynamics.

- 1967–1976 **Adsorption of small molecules on helical gold nanorods: A relativistic density functional study**, Xiao-Jing Liu and Ian Hamilton [Wilfrid Laurier University]

We study the adsorption of a variety of small molecules on helical gold nanorods using relativistic density functional theory. We focus on Au₄₀ which consists of a central linear strand of five gold atoms with seven helical strands of five gold atoms on a coaxial tube. All molecules preferentially adsorb at a single low-coordinated gold atom on the coaxial tube at an end of Au₄₀.

- 1977–1985 **Plane-wave density functional theory investigation of adsorption of 2,4,6-trinitrotoluene on al-hydroxylated (0001) surface of (4×4) α -alumina**, Manoj K. Shukla [US Army Engineer Research and Development Center] and Frances Hill

This article reports the results of the theoretical investigation of adsorption of 2,4,6-trinitrotoluene (TNT) on Al-hydroxylated (0001) surface of (4×4) α -alumina (α -Al₂O₃) using plane-wave Density Functional Theory.

- 1986–1996 **Effects of system net charge and electrostatic truncation on all-atom constant pH molecular dynamics**, Wei Chen and Jana K. Shen [University of Maryland, Baltimore]

See Applications / Protein Dynamics.

Journal of Computational Chemistry, 35 (28), October, 2014.

- 2019–2026 **Kinetics of radical-molecule reactions in aqueous solution: A benchmark study of the performance of density functional methods**, Annia Galano [Universidad Autónoma Metropolitana-Iztapalapa] and Juan Raúl Alvarez-Idaboy

The performance of 18 density functional approximations has been tested for a very challenging task, the calculations of rate constants for radical-molecule reactions in aqueous solution. Despite of the many difficulties involved in such an enterprise, six of them provide high quality results, and are recommended to that purpose. They are LC- ω PBE, M06-2X, BMK, B2PLYP, M05-2X, and MN12SX, in that order.

- 2027–2039 **SLIM: An improved generalized Born implicit membrane model**, Julia Setzler, Carolin Seith, Martin Brieg and Wolfgang Wenzel [Karlsruhe Institute of Technology (KIT)]

In most implicit continuum models, membranes are represented as heterogeneous dielectric environments, but their treatment within computationally efficient generalized Born (GB) models is challenging. A novel scheme (SLIM) to decompose one environment consisting of multiple dielectric regions into a sum of multiple environments consisting only of two dielectric regions each is proposed to solve this issue. These simpler environments can be treated with established GB methods.

- 2040–2046 **Predicting backbone ϕ angles and dihedrals from protein sequences by stacked sparse auto-encoder deep neural network**, James Lyons, Abdollah Dehzangi, Rhys Heffernan, Alok Sharma, Kuldip Paliwal, Abdul Sattar, Yaoqi Zhou and Yuedong Yang [Griffith University]

See Applications / Protein Dynamics.

- 2047–2055 **Importance of cytochromes in cyclization reactions: Quantum chemical study on a model reaction of proguanil to cycloguanil**, Minhajul Arfeen, Dhilon S. Patel, Sheenu Abbat, Nikhil Taxak and Prasad V. Bharatam [National Institute of Pharmaceutical Education and Research (NIPER)]

See Applications / Medicinal Chemistry and Drug Design.

- 2056–2069 **Resolutions of the Coulomb operator: VIII. Parallel implementation using the modern programming language X10**, Taweetham Limpanuparb [Mahidol University, Phutthamonthon], Josh Milthorpe and Alistair P. Rendell

Use of the modern parallel programming language X10 for computing long-range Coulomb and exchange interactions is presented. By using X10, a partitioned global address space language with support for task parallelism and the explicit representation of data locality, the resolution of the Ewald operator can be parallelized in a straightforward manner including use of both intranode and internode parallelism.

- 2070–2075 **Predicting hydration energies for multivalent ions**, Martin P. Andersson [University of Copenhagen, Universitetsparken 5] and Susan L. S. Stipp

We have predicted the free energy of hydration for 40 monovalent and multivalent cations and anions using density functional theory and the implicit solvent model COnductor like Screening MOdel for Real Solvents (COSMO-RS) at the Becke-Perdew (BP)/Triple zeta valence with polarization functions (TZVP) level.

Journal of Molecular Modeling, 20 (10), October, 2014.

- 2476 **Antioxidant activity of flavonoids: a QSAR modeling using Fukui indices descriptors**, Houria Djeradi [University of Bechar], Ali Rahmouni, Abdelkrim Cheriti

See Applications / QSAR.

- 2475 **Theoretical investigation on mechanism and kinetics of the Cl-initiated hydrogen abstraction reactions of ethyl trifluoroacetate at 298 K**, Bhupesh Kumar Mishra [Tezpur University], Hari Ji Singh, Laxmi Tiwari

Theoretical investigations were carried out on the gas-phase reactions of $\text{CF}_3\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, ethyl trifluoroacetate (ETFA) with Cl atoms by means of modern density functional theory methods. The optimized geometries, frequencies and minimum energy path were obtained with the hybrid density functional model MPWB1K using the 6-31+G(d,p) basis set.

- 2474 **Mechanistic aspects of superacid mediated condensation of polyphenols with ketones. Implications for polymer synthesis**, Gustavo López, Olivia H. Cruz, Lilian I. Olvera Garza, Mikhail G. Zolotukhin, Serguei Fomine [Universidad Nacional Autónoma de México]

A detailed computational study of possible reaction paths for methanesulfonic and triflic acid mediated polyhydroxyalkylation reaction between resorcinol and trifluoroacetone accompanied by cyclodehydration to give 9H-xanthene containing polymers has been carried out at M06-2X/6-311+G** level of theory.

- 2471 **Hydration gibbs free energies of open and closed shell trivalent lanthanide and actinide cations from polarizable molecular dynamics**, Aude Marjolin, Christophe Gourlaouen, Carine Clavaguéra, Pengyu Y. Ren, Jean-Philip Piquemal, Jean-Pierre Dognon [CNRS UMR 3299]

The hydration free energies, structures, and dynamics of open- and closed-shell trivalent lanthanide and actinide metal cations are studied using molecular dynamics simulations (MD) based on a polarizable force field.

- 2470 **Molecular modeling and simulation of the human eNOS reductase domain, an enzyme involved in the release of vascular nitric oxide**, N. T. Devika, Prakash Amresh, Md. Imtiyaz Hassan, B. M. Jaffar Ali [Jamia Millia Islamia]

See Methodology / Homology Modeling.

- 2469 **Multiscale molecular dynamics simulations of sodium dodecyl sulfate micelles: from coarse-grained to all-atom resolution**, Guillaume Roussel [University of Namur], Catherine Michaux, Eric A. Perpète

Sodium dodecyl sulfate (SDS) is a well-known anionic detergent widely used in both experimental and theoretical investigations. We propose a new set of parameters for CG, UA, and AA resolutions based on a high quantum mechanics (QM) level optimization of the detergent structure and the charge distribution.

- 2468 **Separation of a heavy metal from water through a membrane containing boron nitride nanotubes: molecular dynamics simulations**, Jafar Azamat, Alireza Khataee, Sang Woo Joo [Yeungnam University]

Molecular dynamics simulations were performed to investigate the separation of zinc ions as a heavy metal from water using boron nitride nanotubes. The studied systems included boron nitride (BN) nanotubes embedded in a silicon-nitride membrane immersed in an aqueous solution of ZnCl_2 .

- 2467 **Density functional study of molecular nitrogen adsorption on gold-copper and gold-silver binary clusters**, Shuang Zhao, XinZhe Tian, JunNa Liu, YunLai Ren, JianJi Wang [Henan University of Science and Technology]

Density functional theory calculations were performed to investigate the adsorption behaviors of nitrogen molecule on small bimetallic Au_nCu_m and Au_nAg_m clusters, with $n + m \leq 5$. In all cases the N_2 forms a linear or quasi-linear M-N-N structure (M = Au, Cu or Ag).

- 2466 **Reaction of Np atom with H_2O in the gas phase: reaction mechanisms and ab initio molecular dynamics study**, Peng Li, Wenxia Niu, Tao Gao [Sichuan University], Hongyan Wang

The gas-phase reaction of an Np atom with H_2O was investigated using density functional theory and ab initio molecular dynamics. The reaction mechanisms and the corresponding potential energy profiles for different possible spin states were analyzed.

- 2465 **Why strategies to control Leishmania spp. multiplication based on the use of proteinase inhibitors should consider multiple targets and not only a single enzyme**, Carlos Roberto Alves [Instituto Oswaldo Cruz], Bernardo Acácio Santini Pereira, Mariana Silva-Almeida, Franklin Souza da Silva

The use of proteinases as targets to develop novel chemotherapies against Leishmania spp. infections is a very promising strategy. Based on a previous study by Goyal et al. [J Mol Model (2014) 20:2099], we discuss herein the idea that only a combined treatment with distinct proteinase inhibitors would be an effective antileishmanial therapy.

- 2463 **Triptan partition in model membranes**, Irene Wood, Mónica Pickholz [Universidad de Buenos Aires]

See Applications / Membrane Proteins and Lipid peptide Interactions.

- 2461 **The effect of HNS on the reinforcement of TNT crystal: a molecular simulation study**, Wen Qian, Yuanjie Shu [Xi'an Modern Chemistry Research Institute], Huarong Li, Qing Ma
- The effect of crystal modifier 2,2',4,4',6,6'-hexanitrostilbene(HNS) on the reinforcement of crystalline 1,3,5-trinitrotoluene (TNT) was investigated by molecular simulation. The intermolecular interactions between HNS and TNT were revealed by quantum chemistry calculations in detail, strong attractive forces were found between HNS and TNT.
- 2460 **Theoretical investigations on charge-transfer properties of pentacenequinone derivatives as n-type organic semiconductors**, Jun Yin, Yong Hu, Xue-Hai Ju [Nanjing University of Science and Technology]
- Electron mobilities of two pentacenequinone derivatives as n-type organic semiconductors, 5,7,12,14-tetraaza-6,13-pentacenequinone (TAPQ5) and 1,4,8,11-tetraaza-6,13-pentacenequinone (TAPQ7), have been investigated at the molecular and crystal levels by means of the density functional theory (DFT) calculations and the incoherent charge-hopping model.
- 2459 **Structural characteristics of liquid nitromethane at the nanoscale confinement in carbon nanotubes**, Yingzhe Liu [Xi'an Modern Chemistry Research Institute], Weipeng Lai, Tao Yu, Zhongxue Ge, Ying Kang
- See Applications / Carbon Nanoparticles.**
- 2458 **Interplay between halogen and chalcogen bonding in the $\text{XCl}\cdots\text{OCS}\cdots\text{NH}_3$ ($\text{X} = \text{F}, \text{OH}, \text{NC}, \text{CN}$, and FCC) complex**, Qiang Zhao [Zibo Vocational Institute]
- The interplay between halogen and chalcogen bonding in the $\text{XCl}\cdots\text{OCS}$ and $\text{XCl}\cdots\text{OCS}\cdots\text{NH}_3$ ($\text{X} = \text{F}, \text{OH}, \text{NC}, \text{CN}$, and FCC) complex was studied at the MP2/6-311++G(d,p) computational level. Cooperative effect is observed when halogen and chalcogen bonding coexist in the same complex. The effect is studied by means of binding distance, interaction energy, and cooperative energy.
- 2457 **Theoretical study on the tautomerization of 1,5-diaminotetrazole (DAT)**, Piao He, Jian-Guo Zhang [Beijing Institute of Technology], Li-Na Feng, Kun Wang, Tong-Lai Zhang, Shao-Wen Zhang
- The tautomerization pathways and kinetics of 1,5-diaminotetrazole (DAT) have been investigated by means of second-order Møller-Plesset perturbation theory (MP2) and coupled-cluster theory, with single and double excitations including perturbative corrections for triple excitations (CCSD(T)).
- 2456 **Utilization of theoretical studies of the imprinting ratio to guide experimental research into the molecular imprinted polymers formed using enrofloxacin and methacrylic acid**, Junbo Liu, Zhengqiang Dai, Bo Li, Shanshan Tang [Jilin Agricultural University], Ruifa Jin
- Computational approaches have been suggested as rational and fast methods for optimizing imprinting ratios. The B3LYP/6-31 g(d,p) level was applied to simulate the self-assembled system of molecularly imprinted polymers (MIPs) formed by enrofloxacin (ENRO) and methacrylic acid (MAA).
- 2455 **Bonding analysis of the donor-acceptor sandwiches CpE-MCp ($\text{E} = \text{B}, \text{Al}, \text{Ga}$; $\text{M} = \text{Li}, \text{Na}, \text{K}$; $\text{Cp} = \eta^5\text{-C}_5\text{H}_5$)**, Suhong Huo, Decheng Meng, Xiayan Zhang, Lingpeng Meng, Xiaoyan Li [Hebei Normal University]
- The nature of E-M bonds in CpE-MCp ($\text{E} = \text{B}, \text{Al}, \text{Ga}$; $\text{M} = \text{Li}, \text{Na}, \text{K}$; $\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) donor-acceptor sandwiches was studied using the atoms in molecules (AIM) theory, electron localization function (ELF), energy decomposition analysis (EDA), and natural bond orbital analysis (NBO) methods.

- 2454 **Oxygen reduction reaction on Cu-doped Ag cluster for fuel-cell cathode**, Wenqiang Ma [Northwestern Polytechnical University], Fuyi Chen, Nan Zhang, Xiaoqiang Wu

The development of fuel cells as clean-energy technologies is largely limited by the prohibitive cost of the noble-metal catalysts needed for catalyzing the oxygen reduction reaction (ORR) in fuel cells. Here, we present a first-principles study of ORR on Ag₁₂Cu cluster in alkaline environment.

- 2453 **On the electron affinity of cytosine in bulk water and at hydrophobic aqueous interfaces**, Esteban Vöhringer-Martinez [Universität Leipzig], Ciro Dörner, Bernd Abel

See Methodology / QM and QM/MM.

- 2452 **Hybrid coarse-grained/atomistic model of “chitosan + carbon nanostructures” composites**, Elena L. Kossovich, Irina V. Kirillova, Leonid Yu. Kossovich, Roman A. Safonov, Dmitriy V. Ukrainskiy, Svetlana A. Apshstein [Moscow State Mining University]

We present a new hybrid molecular dynamics model of chitosan oligomers which is constructed specifically for studying chitosan + carbon nanostructures composites, their structure and mechanical properties. The model is derived for application within the modified molecular mechanics force field AMBER.

- 2451 **Novel theoretically designed HIV-1 non-nucleoside reverse transcriptase inhibitors derived from nevirapine**, Jinfeng Liu, Xiao He [East China Normal University], John Z. H. Zhang

See Methodology / Molecular Dynamics.

- 2450 **Analysis of the structure and dynamics of human serum albumin**, T. R. Cuya Guizado [Pontifical Catholic University of Rio de Janeiro]

See Applications / Protein Structure Analysis.

- 2446 **Combined docking, molecular dynamics simulations and spectroscopic studies for the rational design of a dipeptide ligand for affinity chromatography separation of human serum albumin**, Elham Aghaee, Jahan B. Ghasemi [KN Toosi University of Technology], Firouzeh Manouchehri, Saeed Balalaie

See Methodology / Ligand Docking.

- 2445 **A post-HF study on the interaction of iodine with small polyaromatic hydrocarbons**, Berkay Sütay, Mine Yurtsever, Ersin Yurtsever [Koç University]

In this work, we present a theoretical study of the interaction between a diatomic iodine molecule with planar naphthalene and several other small polyaromatic hydrocarbons (PAHs). Our aim was to understand the general characteristics of the potential energy surface (PES) of this system; that is locating various local minima, finding the variation of PES around these optimum points by means of first principle calculations at MP2, SCS-MP2 and CCSD(T) levels of theory.

- 2443 **Probing the electronic structures and properties of neutral and charged arsenic sulfides [As_nS₂^(-1,0,+1), n = 1–6] with Gaussian-3 theory**, Liyuan Hou, Jucai Yang, Hongmei Ning [Inner Mongolia University of Technology]

The structures and energies of neutral and charged arsenic sulfides As_nS₂^(-1,0,+1) (n = 1–6) were investigated systematically by means of the Gaussian-3 (G3) scheme. The ground-state structures of these species are presented. The ground-state structures of As_nS₂ can be viewed as the lowest-energy structure of neutral As_{n+1}S by replacing an As atom with a S atom.

- 2442 **Theoretical study of polaron binding energy in conformationally disrupted oligosilanes**, Barbora Hanulíková [University Institute, Nad Ovcírnou 3685], Ivo Kuritka

See Applications / Ligand Binding.

- 2438 **Thermal decomposition of solid phase nitromethane under various heating rates and target temperatures based on ab initio molecular dynamics simulations**, Kai Xu, Dong-Qing Wei, Xiang-Rong Chen [Sichuan University], Guang-Fu Ji

The Car-Parrinello molecular dynamics simulation was applied to study the thermal decomposition of solid phase nitromethane under gradual heating and fast annealing conditions. In gradual heating simulations, we found that, rather than C–N bond cleavage, intermolecular proton transfer is more likely to be the first reaction in the decomposition process.

- 2437 **Injection, transport, absorption and phosphorescence properties of a series of platinum (II) complexes with N-heterocyclic carbenes: a DFT and time-dependent DFT study**, Leijiao Li, Xiaojuan Liu, Jing Feng, Shuyan Song, Hongjie Zhang [Changchun Institute of Applied Chemistry]

The ground and excited states, charge injection/transport, and phosphorescence properties of five N-heterocyclic carbene-functionalized Pt^{II} complexes were investigated by using the DFT method. By analyzing the nonradiative (k_{nr}) rate constant and energies at S₀T₀ and T₁T₁ states, it is possible to forecast that BC5 with the pyrrole ligand has a higher phosphorescence quantum yield than any of the other four complexes.

- 2433 **Bonding analysis of telluroketones H₂A=Te (A = C, Si, Ge)**, Naziah B. Jaufeerally, Ponnadurai Ramasami, Paul Jerabek, Gernot Frenking [Philipps-Universität Marburg]

Quantum chemical calculations using density functional theory BP86/def2-TZVPP and ab initio methods at CCSD(T)/def2-TZVPP have been carried for the telluroketones H₂A=Te (A = C, Si, Ge). DFT calculations have also been carried out for the ketones H₂C=E (E = O, S, Se, Te) and for the complexes NHC → [H₂A=Te] → B(C₆F₅)₃.

- 2420 **Application of 4D-QSAR studies to a series of benzothiophene analogs**, Giovana Baptista Caldas, Teodorico C. Ramalho, Elaine F. F. da Cunha [Federal University of Lavras]

Four-dimensional quantitative structure-activity relationship (4D-QSAR) analysis was applied to a series of 52 benzothiophene analogs synthesized by Hiroshi Yamashita et al. (2011, United States Patent no. US8,349,840) and evaluated as dopamine D₂ receptor inhibitors.

4. ADDRESSES OF PRINCIPAL AUTHORS

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About 120 Papers from more than 30 Journals are cited.

1 APPLICATIONS (89) Page 2

1.1 Small Molecules (15)

General and Model Systems	Page 2	QSAR	Page 6
Med. Chem. And Drug Design	Page 2	Carbon Nanoparticles	Page 6

1.2 Biopolymers (74)

Bioinformatics and Cheminformatics	Page 6	Ligand Binding	Page 18
Protein Secondary Structure	Page 9	Enzyme Catalysis	Page 19
Comparative or Homology Modeling	Page 9	Protein-Protein Interactions	Page 22
Protein Conformational Analysis	Page 10	Membrane Proteins	Page 22
Protein Structure Analysis	Page 13	Protein Folding	Page 25
Protein Dynamics	Page 14	Protein-Nucleic Acids	Page 25
Free Energy Calculations	Page 17	Nucleic Acids	Page 26

1.3 Polymers

1.4 Surfaces, Catalysts and Material Page 27

2 METHODOLOGY (28) Page 28

Potentials and Parameters	Page 28	Monte Carlo	Page 32
Solvation Energy	Page 29	QM & QM/MM Modeling	Page 32
Molecular Dynamics	Page 30	Ligand Docking	Page 34

3 JOURNAL REVIEWS (5) Page 37

Journal of Computational Chemistry, 35 (29), November, 2014.
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 Journal of Computational Chemistry, 35 (31), December, 2014.
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4 ADDRESSES OF PRINCIPAL AUTHORS Page 48

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1. APPLICATIONS

1.1. Small Molecules

General and Model Systems

Monte Carlo simulation of mixed nonionic Brij surfactants in water

Ruzanna Yahya, Roghayeh Abedi Karjiban [Universiti Putra Malaysia], Mahiran Basri, Mohd Basyaruddin Abdul Rahman, Mauricio Girardi

J. Mol.Mod., **20**, 2512, 2014.

Nonionic surfactants such as the Brij® series are important in the preparation of transdermal drug nanodelivery products using nanoemulsions because of their low toxicity and low irritancy. Here, Monte Carlo (MC) simulation was used to examine the physical behavior of the model deterministic system by using sampling procedures. Metropolis MC simulations were run on three mixtures of two different nonionic surfactants, Brij92 and Brij96, with different compositions in aqueous solution.

Medicinal Chemistry and Drug Design

Discovery of novel covalent proteasome inhibitors through a combination of pharmacophore screening, covalent docking, and molecular dynamics simulations

Aibo Li, Haopeng Sun, Lei Du, Xiaoxin Wu, Jianqin Cao, Qidong You, Yuyan Li [China Pharmaceutical University]

J. Mol.Mod., **20**, 2515, 2014.

The ubiquitin–proteasome pathway plays a pivotal role in the regulation of cellular protein processing and degradation. Proteasome inhibitors (PIs) have enormous potential to treat multiple myeloma, solid tumors, parasites, inflammation, and immune diseases, which is spurring the development of new types of PIs with enhanced efficacy, fewer side effects, and reduced drug resistance. Nevertheless, virtual screening for covalent PIs has rarely been reported because calculating the covalent binding energy is a challenging task. The aim of this study was to discover new covalent inhibitors of the 20S proteasome.



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Medicinal Chemistry and Drug Design (Cont'd)

Three model shapes of Doxorubicin for liposome encapsulation

Kanes Sumetpipat [Mahidol University], Duangkamon Baowan

J. Mol.Mod., **20**, 2504, 2014.

Targeted drug delivery provides a possible method for the transfer of drug molecules into cancer cells. Liposomes together with a drug, such as Doxorubicin (DOX) inside the liposomes, can be formed as a nano-capsule. In this study, we are interested in finding a favorable size of liposome and an appropriate shape of DOX cluster: sphere, cylinder or ellipsoid. Using mathematical modeling, the interaction energy of the system is obtained from the Lennard-Jones potential and the continuum assumption which assumes that discrete atomic structure can be replaced by an average atomic density spread over a surface.

Emulating structural stability of *Pseudomonas mendocina* lipase: in silico mutagenesis and molecular dynamics studies

Parameswaran Saravanan, Vikash Kumar Dubey, Sanjukta Patra [Indian Institute of Technology Guwahati]

J. Mol.Mod., **20**, 2501, 2014.

The need of alkaline detergent-stable lipases has been growing rapidly as they are highly attractive for the production of detergents, biodiesel, pharmaceuticals agents, and various other applications. Lipase from *Pseudomonas mendocina* (PML) is one such candidate with triglyceride activity and non-homologous with other reported *Pseudomonas* lipases. The present work provides insights on the role of amino acids toward structural stability of PML. PML was subjected to mutagenesis through in silico point mutations for emulating its structural stability, the foremost property to enhance biophysiochemical properties for industrial process.

Understanding the effects on constitutive activation and drug binding of a D130N mutation in the $\beta 2$ adrenergic receptor via molecular dynamics simulation

Yanyan Zhu, Yuan Yuan, Xiuchan Xiao, Liyun Zhang, Yanzhi Guo, Xuemei Pu [Sichuan University]

J. Mol.Mod., **20**, 2491, 2014.

G-protein-coupled receptors (GPCRs) are currently one of the largest families of drug targets. The constitutive activation induced by mutation of key GPCR residues is associated closely with various diseases. However, the structural basis underlying such activation and its role in drug binding has remained unclear. Herein, we used all-atom molecular dynamics simulations and free energy calculations to study the effects of a D130N mutation on the structure of $\beta 2$ adrenergic receptor ($\beta 2AR$) and its binding of the agonist salbutamol. The results indicate that the mutation caused significant changes in some key helices.

Deformation density components analysis of fullerene-based anti-HIV drugs

Sara Fakhraee [Payame Noor University], Maryam Souri

J. Mol.Mod., **20**, 2486, 2014.

Deformation density analysis is performed on fullerene-based anti-HIV agents to investigate the influence of charge redistribution on the capability of binding to HIV enzymes. Two types of HIV inhibitors including malonic acid- and amino acid-type C_{60} derivatives are considered to study. Total deformation density and its components including orbital relaxation and kinetic energy pressure are obtained for C_{60} derivatives. The deformation natural orbitals for each component of deformation density are assessed and their amounts of charge displacement are quantified to evaluate the binding affinity of HIV inhibitors.

Medicinal Chemistry and Drug Design (Cont'd)

Identification of Sumoylation Inhibitors Targeting a Predicted Pocket in Ubc9

Ashutosh Kumar, Akihiro Ito, Mikako Hirohama, Minoru Yoshida, and Kam Y. J. Zhang [Center for Life Science Technologies, RIKEN]

J.Chem. Infor. and Mod. **54**, 2784–2793, 2014.

Sumoylation is a post-translational modification that plays an important role in a wide range of cellular processes. Among the proteins involved in the sumoylation pathway, Ubc9 is the sole E2-conjugating enzyme required for sumoylation and plays a central role by interacting with almost all of the partners required for sumoylation. Ubc9 has been implicated in a variety of human malignancies. In order to exploit the therapeutic potential of Ubc9, we have identified the potential site to target for rational drug design using molecular modeling approaches.

Identification of a Novel Inhibitor of Dengue Virus Protease through Use of a Virtual Screening Drug Discovery Web Portal

Usha Viswanathan, Suzanne M. Tomlinson, John M. Fonner, Stephen A. Mock, and Stanley J. Watowich [University of Texas Medical Branch]

J.Chem. Infor. and Mod. **54**, 2816–2825, 2014.

We report the discovery of a novel small-molecule inhibitor of the dengue virus (DENV) protease (NS2B-NS3pro) using a newly constructed Web-based portal (DrugDiscovery@TACC) for structure-based virtual screening. Our drug discovery portal, an extension of virtual screening studies performed using IBM's World Community Grid, facilitated access to supercomputer resources managed by the Texas Advanced Computing Center (TACC) and enabled druglike commercially available small-molecule libraries to be rapidly screened against several high-resolution DENV NS2B-NS3pro crystallographic structures.

Improving *Trichoderma reesei* Cel7B Thermostability by Targeting the Weak Spots

Shujun Zhang, Yefei Wang, Xiangfei Song, Jingbo Hong, Yu Zhang, and Lishan Yao [Qingdao Institute of Bioenergy and Bioprocess Technology Chinese Academy of Sciences]

J.Chem. Infor. and Mod. **54**, 2826–2833, 2014.

For proteins that denature irreversibly, the denaturation is typically triggered by a partial unfolding, followed by a permanent change (e.g., aggregation). The regions that initiate the partial unfolding are named “weak spots”. In this work, a molecular dynamics (MD) simulation and data analysis protocol is developed to identify the weak spots of *Trichoderma reesei* Cel7B, an important endoglucanase in cellulose hydrolysis, through assigning the local melting temperature (T_{mp}) to individual residue pairs.

Application of the 4D Fingerprint Method with a Robust Scoring Function for Scaffold-Hopping and Drug Repurposing Strategies

Adel Hamza, Jonathan M. Wagner, Ning-Ning Wei, Stefan Kwiatkowski, Chang-Guo Zhan, David S. Watt, and Konstantin V. Korotkov [University of Kentucky, Lexington]

J.Chem. Infor. and Mod. **54**, 2834–2845, 2014.

Two factors contribute to the inefficiency associated with screening pharmaceutical library collections as a means of identifying new drugs: [1] the limited success of virtual screening (VS) methods in identifying new scaffolds; [2] the limited accuracy of computational methods in predicting off-target effects. We recently introduced a 3D shape-based similarity algorithm of the SABRE program, which encodes a consensus molecular shape pattern of a set of active ligands into a 4D fingerprint descriptor. Here, we report a mathematical model for shape similarity comparisons and ligand database filtering using this 4D fingerprint method and benchmarked the scoring function HWK (Hamza–Wei–Korotkov), using the 81 targets of the DEKOIS database.

Medicinal Chemistry and Drug Design (Cont'd)

Computational Approaches Elucidate the Allosteric Mechanism of Human Aromatase Inhibition: A Novel Possible Route to Small-Molecule Regulation of CYP450s Activities?

Jacopo Sgrignani, Marta Bon, Giorgio Colombo, and Alessandra Magistrato [CNR-IOM-Democritos National Simulation Center c/o SISSA]

J.Chem. Infor. and Mod. **54**, 2856–2868, 2014.

Human aromatase (HA) is a P450 cytochrome (CYP) with an essential role in estrogen biosynthesis. Since more than 70% of breast cancers are positive for estrogenic receptor (ER), the reduction of estrogen physiological concentrations through HA inhibition is one of most important therapeutic strategies against this cancer type. Recently, experimental evidence showed that selected taxmoxifen metabolites, which are typically used as estrogen receptor modulators (SERMs), inhibit HA through an allosteric mechanism. In this work, we present a computational protocol to (i) characterize the structural framework and (ii) define the atomistic details of the determinants for the noncompetitive inhibition mechanism.

Design of Novel Rho Kinase Inhibitors Using Energy Based Pharmacophore Modeling, Shape-Based Screening, in Silico Virtual Screening, and Biological Evaluation

Ram Kumar Mishra, Reshma Alokam, Sarthak Mohan Singhal, Geethasai Srivathsav, Dharamarajan Sriram, Neerja Kaushik-Basu [Birla Institute of Technology & Science–Pilani], Dinesh Manvar, and Perumal Yogeewari

J.Chem. Infor. and Mod. **54**, 2876–2886, 2014.

Rho-associated protein kinase (ROCK) plays a key role in regulating a variety of cellular processes, and dysregulation of ROCK signaling or expression is implicated in numerous diseases and infections. ROCK proteins have therefore emerged as validated targets for therapeutic intervention in various pathophysiological conditions such as diabetes-related complications or hepatitis C-associated pathogenesis. In this study, we report on the design and identification of novel ROCK inhibitors utilizing energy based pharmacophores and shape-based approaches.

Discovery of Inhibitors of *Schistosoma mansoni* HDAC8 by Combining Homology Modeling, Virtual Screening, and in Vitro Validation

Srinivasaraghavan Kannan, Jelena Melesina, Alexander-Thomas Hauser, Alokta Chakrabarti, Tino Heimburg, Karin Schmidtkunz, Alexandra Walter, Martin Marek, Raymond J. Pierce, Christophe Romier, Manfred Jung, and Wolfgang Sippl [University Halle-Wittenberg]

J.Chem. Infor. and Mod. **54**, 3005–3019, 2014.

Schistosomiasis, caused by *S. mansoni*, is a tropical disease that affects over 200 million people worldwide. A novel approach for targeting eukaryotic parasites is to tackle their dynamic epigenetic machinery that is necessary for the extensive phenotypic changes during their life cycle. We recently identified *S. mansoni* histone deacetylase 8 (smHDAC8) as a potential target for antiparasitic therapy. Here we present results from a virtual screening campaign on smHDAC8. Besides hydroxamates, several sulfonamide-thiazole derivatives were identified by a target-based virtual screening using a homology model of smHDAC8.

Quantitative Structure-Activity Relations

2D and 3D Quantitative Structure–Activity Relationship Study of Hepatitis C Virus NS5B Polymerase Inhibitors by Comparative Molecular Field Analysis and Comparative Molecular Similarity Indices Analysis Methods

Eslam Pourbasheer [Payame Noor University (PNU)], Reza Aalizadeh, Samira Shokouhi Tabar, Mohammad Reza Ganjali, Parviz Norouzi, and Javad Shadmanesh

J.Chem. Infor. and Mod. **54**, 2902–2914, 2014.

In this present study, three-dimensional quantitative structure–activity relationship (3D-QSAR) and 2D-QSAR analyses were performed on the series of compounds Hepatitis C Virus NS5B polymerase inhibitors using comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA), and stepwise multiple linear regression (SW-MLR) approaches. A CoMFA model with good predictive ability was generated based on training set of 39 compounds and showed satisfactory statistical results ($q^2 = 0.600$, $r^2 = 0.871$). To improve the contribution of points for next analyses, CoMFA (after region focusing) was employed in biases of similar alignment and showed appropriate predictive results ($q^2 = 0.691$, $r^2 = 0.889$).

Carbon Nanoparticles

Effects of Hydroxylated Carbon Nanotubes on the Aggregation of A β_{16-22} Peptides: A Combined Simulation and Experimental Study

Luogang Xie, Dongdong Lin, Yin Luo, Huiyu Li, Xinju Yang, Guanghong Wei [Fudan University]

Biophysical Journal. **107**, 1930-1938, 2014.

The pathogenesis of Alzheimer's disease (AD) is associated with the aggregation of amyloid- β (A β) peptides into toxic aggregates with β -sheet character. In a previous computational study, we showed that pristine single-walled carbon nanotubes (SWCNTs) can inhibit the formation of β -sheet-rich oligomers in the central hydrophobic core fragment of A β (A β_{16-22}). However, the poor solubility of SWCNTs in water hinders their use in biomedical applications and nanomedicine. Here, we investigate the influence of hydroxylated SWCNT, a water-soluble SWCNT derivative, on the aggregation of A β_{16-22} peptides using all-atom explicit-water replica exchange molecular dynamics simulations.

1.2. Biopolymers

Bioinformatics and Cheminformatics

Biocellion: accelerating computer simulation of multicellular biological system models

Seunghwa Kang [Pacific Northwest National Laboratory], Simon Kahan, Jason McDermott, Nicholas Flann, and Ilya Shmulevich

Bioinformatics. **30**, 3101-3108, 2014.

Biological system behaviors are often the outcome of complex interactions among a large number of cells and their biotic and abiotic environment. Computational biologists attempt to understand, predict and manipulate biological system behavior through mathematical modeling and computer simulation. We have developed Biocellion, a high-performance software framework, to solve this computing challenge using parallel computers. To support a wide range of multicellular biological system models, Biocellion asks users to provide their model specifics by filling the function body of pre-defined model routines.

Bioinformatics and Cheminformatics (Cont'd)

e-Driver: a novel method to identify protein regions driving cancer

Eduard Porta-Pardo and Adam Godzik [Sanford-Burnham Medical Research Institute]

Bioinformatics. **30**, 3109-3114, 2014.

Most approaches used to identify cancer driver genes focus, true to their name, on entire genes and assume that a gene, treated as one entity, has a specific role in cancer. This approach may be correct to describe effects of gene loss or changes in gene expression; however, mutations may have different effects, depending on which region of the gene they affect. We have developed e-Driver, a method that exploits the internal distribution of somatic missense mutations between the protein's functional regions (domains or intrinsically disordered regions) to find those that show a bias in their mutation rate as compared with other regions of the same protein, providing evidence of positive selection and suggesting that these proteins may be actual cancer drivers.

BioTextQuest⁺: a knowledge integration platform for literature mining and concept discovery

Nikolas Papanikolaou, Georgios A. Pavlopoulos [University of Crete, Medical School], Evangelos Pafilis, Theodosios Theodosiou, Reinhard Schneider, Venkata P. Satagopam, Christos A. Ouzounis, Aristides G. Eliopoulos, Vasilis J. Promponas, and Ioannis Iliopoulos

Bioinformatics. **30**, 3249-3256, 2014.

The iterative process of finding relevant information in biomedical literature and performing bioinformatics analyses might result in an endless loop for an inexperienced user, considering the exponential growth of scientific corpora and the plethora of tools designed to mine PubMed[®] and related biological databases. Herein, we describe BioTextQuest⁺, a web-based interactive knowledge exploration platform with significant advances to its predecessor (BioTextQuest), aiming to bridge processes such as bioentity recognition, functional annotation, document clustering and data integration towards literature mining and concept discovery.

GneimoSim: A modular internal coordinates molecular dynamics simulation package

Adrien B. Larsen, Jeffrey R. Wagner, Saugat Kandel, Romelia Salomon-Ferrer, Nagarajan Vaidehi and Abhinandan Jain [California Institute of Technology]

J. Comp. Chem., **35**, 2245–2255, 2014.

The generalized Newton–Euler inverse mass operator (GNEIMO) method is an advanced method for internal coordinates molecular dynamics (ICMD). GNEIMO includes several theoretical and algorithmic advancements that address longstanding challenges with ICMD simulations. In this article, we describe the GneimoSim ICMD software package that implements the GNEIMO method. We believe that GneimoSim is the first software package to include advanced features such as the equipartition principle derived for internal coordinates, and a method for including the Fixman potential to eliminate systematic statistical biases introduced by the use of hard constraints.

Scents and sense: In silico perspectives on olfactory receptors

Charleen G. Don and Sereina Riniker [Swiss Federal Institute of Technology]

J. Comp. Chem., **35**, 2279–2287, 2014.

Olfactory receptors (ORs) represent the largest subfamily of the superfamily G protein-coupled receptors (GPCRs). This family of membrane receptors functions as essential gateway for activation of many cellular signaling pathways. As no crystal structure of an OR is available yet, homology modeling can be applied to generate a three-dimensional OR model. Molecular docking, molecular dynamics simulations and qualitative structure-activity-relationship can further guide experimental research by investigating interactions at the atomic level.

Bioinformatics and Cheminformatics (Cont'd)

A General Sequence Processing and Analysis Program for Protein Engineering

Ryan L. Stafford [, Sutro Biopharma, Inc.], Erik S. Zimmerman, Trevor J. Hallam, and Aaron K. Sato

J.Chem. Infor. and Mod. **54**, 3020–3032, 2014.

Protein engineering projects often amass numerous raw DNA sequences, but no readily available software combines sequence processing and activity correlation required for efficient lead identification. XLibraryDisplay is an open source program integrated into Microsoft Excel for Windows that automates batch sequence processing via a simple step-by-step, menu-driven graphical user interface. XLibraryDisplay accepts any DNA template which is used as a basis for trimming, filtering, translating, and aligning hundreds to thousands of sequences (raw, FASTA, or Phred PHD file formats).

Lightweight object oriented structure analysis: Tools for building tools to analyze molecular dynamics simulations

Tod D. Romo, Nicholas Leioatts and Alan Grossfield [University of Rochester Medical Center]

J. Comp. Chem., **35**, 2305–2318, 2014.

LOOS (Lightweight Object Oriented Structure-analysis) is a C++ library designed to facilitate making novel tools for analyzing molecular dynamics simulations by abstracting out the repetitive tasks, allowing developers to focus on the scientifically relevant part of the problem. LOOS supports input using the native file formats of most common biomolecular simulation packages, including CHARMM, NAMD, Amber, Tinker, and Gromacs. A dynamic atom selection language based on the C expression syntax is included and is easily accessible to the tool-writer.

Score_set: A CAPRI benchmark for scoring protein complexes

Marc F. Lensink [University Lille North of France] and Shoshana J. Wodak

Proteins: Stru. Fun. & Bioinf., **82**, 3163–3169, 2014.

Critical Assessment of PRedicted Interactions (CAPRI) has proven to be a catalyst for the development of docking algorithms. An essential step in docking is the scoring of predicted binding modes in order to identify stable complexes. In 2005, CAPRI introduced the scoring experiment, where upon completion of a prediction round, a larger set of models predicted by different groups and comprising both correct and incorrect binding modes, is made available to all participants for testing new scoring functions independently from docking calculations. Here we present an expanded benchmark data set for testing scoring functions, which comprises the consolidated ensemble of predicted complexes made available in the CAPRI scoring experiment since its inception.

Protein Secondary Structure

Virtual screening on an α -helix to β -strand switchable region of the FGFR2 extracellular domain revealed positive and negative modulators

Constantino Diaz [Sanofi-Aventis Research and Development], Herbert Corentin, Verinat Thierry, Alcouffe Chantal, Bozec Tanguy, Sibrac David, Herbert Jean-Marc, Ferrara Pascual, Bono Françoise and Ferran Edgardo

Proteins: Stru. Fun. & Bioinf., **82**, 2982–2997, 2014.

The secondary structure of some protein segments may vary between α -helix and β -strand. To predict these switchable segments, we have developed an algorithm, Switch-P, based solely on the protein sequence. This algorithm was used on the extracellular parts of FGF receptors. For FGFR2, it predicted that β 4 and β 5 strands of the third Ig-like domain were highly switchable. These two strands possess a high number of somatic mutations associated with cancer. Analysis of PDB structures of FGF receptors confirmed the switchability prediction for β 5. We thus evaluated if compound-driven α -helix/ β -strand switching of β 5 could modulate FGFR2 signaling.

Helix stability of oligoglycine, oligoalanine, and oligo- β -alanine dodecamers reflected by hydrogen-bond persistence

Chengyu Liu, Jay W. Ponder and Garland R. Marshall [Washington University, St. Louis]

Proteins: Stru. Fun. & Bioinf., **82**, 3043–3061, 2014.

Helices are important structural/recognition elements in proteins and peptides. Stability and conformational differences between helices composed of α - and β -amino acids as scaffolds for mimicry of helix recognition has become a theme in medicinal chemistry. Furthermore, helices formed by β -amino acids are experimentally more stable than those formed by α -amino acids. This is paradoxical because the larger sizes of the hydrogen-bonding rings required by the extra methylene groups should lead to entropic destabilization. In this study, molecular dynamics simulations using the second-generation force field, explored the stability and hydrogen-bonding patterns of capped oligo- β -alanine, oligoalanine, and oligoglycine dodecamers in water.

Comparative or Homology Modeling

Molecular Dynamics Simulations of Structure–Property Relationships of Tween 80 Surfactants in Water and at Interfaces

Xueming Tang, Kyle J. Huston, and Ronald G. Larson [University of Michigan, Ann Arbor]

J. Phys. Chem. B., **118**, 12907–12918, 2014.

We build a united atom model for Tween 80 (polyoxyethylene sorbitan oleates), based on the GROMOS53A6_{OXY+D} force field, and apply it to two stereoisomers, three constitutional isomers, and three structures with one, two, and three tails, to represent components in the Tween 80 commercial mixture. In a preassembled micelle containing 60 molecules, the distribution of Tween tail and ethylene oxide head groups is found to be insensitive to stereoisomerization but sensitive to changes in relative lengths of the four polyoxyethylene head groups.

Protein Conformational Analysis

Molecular Dynamics Simulations Identify Time Scale of Conformational Changes Responsible for Conformational Selection in Molecular Recognition of HIV-1 Transactivation Responsive RNA

Francesco Musiani, Giulia Rossetti, Luciana Capece, Thomas Martin Gerger, Cristian Micheletti, Gabriele Varani, and Paolo Carloni [German Research School for Simulation Sciences]

J. Am. Chem. Soc., 2013, **136**, 15631–15637, 2014.

The HIV-1 Tat protein and several small molecules bind to HIV-1 transactivation responsive RNA (TAR) by selecting sparsely populated but pre-existing conformations. Thus, a complete characterization of TAR conformational ensemble and dynamics is crucial to understand this paradigmatic system and could facilitate the discovery of new antivirals targeting this essential regulatory element. We show here that molecular dynamics simulations can be effectively used toward this goal by bridging the gap between functionally relevant time scales that are inaccessible to current experimental techniques.

A Functional Selectivity Mechanism at the Serotonin-2A GPCR Involves Ligand-Dependent Conformations of Intracellular Loop 2

Jose Manuel Perez-Aguilar, Jufang Shan, Michael V. LeVine, George Khelashvili, and Harel Weinstein [Weill Medical College of Cornell University]

J. Am. Chem. Soc., 2013, **136**, 16044–16054, 2014.

With recent progress in determination of G protein-coupled receptor (GPCR) structure with crystallography, a variety of other experimental approaches (e.g., NMR spectroscopy, fluorescent-based assays, mass spectrometry techniques) are also being used to characterize state-specific and ligand-specific conformational states. MD simulations offer a powerful complementary approach to elucidate the dynamic features associated with ligand-specific GPCR conformations.

Molecular dynamics simulation of configurational ensembles compatible with experimental FRET efficiency data through a restraint on instantaneous FRET efficiencies

Maria M. Reif and Chris Oostenbrink [University of Natural Resources and Life Sciences]

J. Comp. Chem., **35**, 2319–2332, 2014.

Förster resonance energy transfer (FRET) measurements are widely used to investigate (bio)molecular interactions or/and association. FRET efficiencies, the primary data obtained from this method, give, in combination with the common assumption of isotropic chromophore orientation, detailed insight into the lengthscale of molecular phenomena. This study illustrates the application of a FRET efficiency restraint during classical atomistic molecular dynamics simulations of a mutant mastoparan X peptide in either water or 7 M aqueous urea.

Conformation and dynamics of 8-Arg-vasopressin in solution

Elke Haensele, Lee Banting, David C. Whitley, Timothy Clark [University of Portsmouth]

J. Mol.Mod., **20**, 2485, 2014.

Arginine-vasopressin was subjected to a long (11 μ s) molecular dynamics simulation in aqueous solution. Analysis of the results by DASH and principal components analyses revealed four main ring conformations that move essentially independently of the faster-moving tail region. Two of these conformations (labeled “saddle”) feature well-defined β -turns in the ring and conserved transannular hydrogen bonds, whereas the other two (“open”) feature neither.

Protein Conformational Analysis (Cont'd)

Conformational analysis of a polyconjugated protein-binding ligand by joint quantum chemistry and polarizable molecular mechanics. Addressing the issues of anisotropy, conjugation, polarization, and multipole transferability

Elodie Goldwaser, Benoit de Courcy, Luc Demange, Christiane Garbay, Françoise Raynaud, Reda Hadj-Slimane, Jean-Philip Piquemal, Nohad Gresh [Université ParisDescartes]

J. Mol.Mod., **20**, 2472, 2014.

We investigate the conformational properties of a potent inhibitor of neuropilin-1, a protein involved in cancer processes and macular degeneration. This inhibitor consists of four aromatic/conjugated fragments: a benzimidazole, a methylbenzene, a carboxythiourea, and a benzene-linker dioxane, and these fragments are all linked together by conjugated bonds. The calculations use the SIBFA polarizable molecular mechanics procedure. Prior to docking simulations, it is essential to ensure that variations in the ligand conformational energy upon rotations around its six main-chain torsional bonds are correctly represented.

Accelerating the Conformational Sampling of Intrinsically Disordered Proteins

Trang Nhu Do, Wing-Yiu Choy, and Mikko Karttunen [Waterloo Institute for Nanotechnology]

J. Chem. Theor. and Comp., **10**, 5081–5094, 2014.

Intrinsically disordered proteins (IDPs) are a class of proteins lacking a well-defined secondary structure. Instead, they are able to attain multiple conformations, bind to multiple targets, and respond to changes in their surroundings. Functionally, IDPs have been associated with molecular recognition, cell regulation, and signal transduction. The dynamic conformational ensemble of IDPs is highly environmental and binding partner dependent, rendering the characterization of IDPs extremely challenging. Here, we compare the sampling efficiencies of conventional molecular dynamics (MD), well-tempered metadynamics (WT-META), and bias-exchange metadynamics (BE-META).

Assessing an Ensemble Docking-Based Virtual Screening Strategy for Kinase Targets by Considering Protein Flexibility

Sheng Tian, Huiyong Sun, Peichen Pan, Dan Li, Xuechu Zhen, Youyong Li, and Tingjun Hou [Soochow University]

J.Chem. Infor. and Mod. **54**, 2664–2679, 2014.

In this study, to accommodate receptor flexibility, based on multiple receptor conformations, a novel ensemble docking protocol was developed by using the naïve Bayesian classification technique, and it was evaluated in terms of the prediction accuracy of docking-based virtual screening (VS) of three important targets in the kinase family: ALK, CDK2, and VEGFR2. First, for each target, the representative crystal structures were selected by structural clustering, and the capability of molecular docking based on each representative structure to discriminate inhibitors from non-inhibitors was examined.

Exploring Protein Kinase Conformation Using Swarm-Enhanced Sampling Molecular Dynamics

Alessio Atzori, Neil J. Bruce, Kepa K. Burusco, Berthold Wroblowski, Pascal Bonnet, and Richard A. Bryce [University of Manchester, Oxford Road]

J.Chem. Infor. and Mod. **54**, 2764–2775, 2014.

Protein plasticity, while often linked to biological function, also provides opportunities for rational design of selective and potent inhibitors of their function. The application of computational methods to the prediction of concealed protein concavities is challenging, as the motions involved can be significant and occur over long time scales. Here we introduce the swarm-enhanced sampling molecular dynamics (sesMD) method as a tool to improve sampling of conformational landscapes. In this approach, a swarm of replica simulations interact cooperatively via a set of pairwise potentials incorporating attractive and repulsive components.

Protein Conformational Analysis (Cont'd)

Predicting Order and Disorder for β -Peptide Foldamers in Water

Lukács J. Németh, Zsófia Hegedűs, and Tamás A. Martinek [University of Szeged]

J.Chem. Infor. and Mod. **54**, 2776–2783, 2014.

Following a quantitative validation approach, we tested the AMBER ff03 and GAFF force fields with the TIP3P explicit water model in molecular dynamic simulations of β -peptide foldamers. The test sequences were selected to represent a wide range of folding behavior in water: compact helix, strand mimetic geometry, and the state of disorder. The combination AMBER ff03–TIP3P successfully predicted the experimentally observed conformational properties and reproduced the NOE distances and backbone ^3J coupling data at a good level.

Understanding the apparent stator-rotor connections in the rotary ATPase family using coarse-grained computer modeling

Robin A. Richardson, Konstantinos Papachristos, Daniel J. Read, Oliver G. Harlen, Michael Harrison, Emanuele Paci, Stephen P. Muench and Sarah A. Harri [University of Leeds, Leeds]

Proteins: Stru. Fun. & Bioinf., **82**, 3298–3311, 2014.

Advances in structural biology, such as cryo-electron microscopy (cryo-EM) have allowed for a number of sophisticated protein complexes to be characterized. However, often only a static snapshot of a protein complex is visualized despite the fact that conformational change is frequently inherent to biological function, as is the case for molecular motors. Here we compare ENM with a recently proposed continuum model known as Fluctuating Finite Element Analysis (FFEA), which represents the biomolecule as a viscoelastic solid subject to thermal fluctuations. These two complementary computational techniques are used to answer a critical question in the rotary ATPase family; implicit within these motors is the need for a rotor axle and proton pump to rotate freely of the motor domain and stator structures.

Hamiltonian replica exchange combined with elastic network analysis to enhance global domain motions in atomistic molecular dynamics simulations

Katja Ostermeir and Martin Zacharias [Technische Universität München]

Proteins: Stru. Fun. & Bioinf., **82**, 3410–3419, 2014.

Coarse-grained elastic network models (ENM) of proteins offer a low-resolution representation of protein dynamics and directions of global mobility. A Hamiltonian-replica exchange molecular dynamics (H-REMD) approach has been developed that combines information extracted from an ENM analysis with atomistic explicit solvent MD simulations. Based on a set of centers representing rigid segments (centroids) of a protein, a distance-dependent biasing potential is constructed by means of an ENM analysis to promote and guide centroid/domain rearrangements. The biasing potentials are added with different magnitude to the force field description of the MD simulation along the replicas with one reference replica under the control of the original force field.

Protein Structure Analysis

CCMpred—fast and precise prediction of protein residue–residue contacts from correlated mutations

Stefan Seemayer, Markus Gruber, and Johannes Söding
[Gene Center, LMU Munich]

Bioinformatics. **30**, 3128–3130, 2014.

Recent breakthroughs in protein residue–residue contact prediction have made reliable de novo prediction of protein structures possible. The key was to apply statistical methods that can distinguish direct couplings between pairs of columns in a multiple sequence alignment from merely correlated pairs, i.e. to separate direct from indirect effects. Here we introduce CCMpred, our performance-optimized PLM implementation in C and CUDA C. Using graphics cards in the price range of current six-core processors, CCMpred can predict contacts for typical alignments 35–113 times faster and with the same precision as the most accurate published methods.

Terahertz Chiroptical Spectroscopy of an α -Helical Polypeptide: A Molecular Dynamics Simulation Study

Jun-Ho Choi and Minhaeng Cho [Korea University, Seoul]

J. Phys. Chem. B, **118**, 12837–12843, 2014.

Vibrational spectroscopy has provided incisive information on the structure of biological molecules. Here, using a molecular dynamics simulation method, infrared vibrational circular dichroism and vibrational optical rotatory dispersion spectra of a right-handed α -helix in the terahertz (THz) frequency range are calculated. Both the autocorrelation function of an electric dipole moment and the cross-correlation function of electric and magnetic dipole moments of the α -helix are calculated and Fourier-transformed to obtain THz absorption and optical activity spectra, which reveal characteristic features of the helical polypeptide structure.

R102Q Mutation Shifts the Salt-Bridge Network and Reduces the Structural Flexibility of Human Neuronal Calcium Sensor-1 Protein

Yuzhen Zhu, Ying Wu, Yin Luo, Yu Zou, Buyong Ma, and Qingwen Zhang [Shanghai University of Sport]

J. Phys. Chem. B, **118**, 13112–13122, 2014.

Neuronal calcium sensor-1 (NCS-1) protein has a variety of different neuronal functions and interacts with multiple binding partners mostly through a large solvent-exposed hydrophobic crevice (HC). A single R102Q mutation in human NCS-1 protein was demonstrated to be associated with autism disease. Solution NMR study reported that this R102Q mutant had long-range chemical shift effects on the HC and the C-terminal tail (L3). To understand the influence of the R102Q mutation on the HC and L3 of NCS-1, we have investigated the conformational dynamics and the structural flexibility of wild type (WT) NCS-1 and its R102Q mutant by conducting extensive all-atom molecular dynamics (MD) simulations.

Protein Dynamics

Remodeling of Fibrous Extracellular Matrices by Contractile Cells: Predictions from Discrete Fiber Network Simulations

A.S. Abhilash, Brendon M. Baker, Britta Trappmann, Christopher S. Chen, Vivek B. Shenoy [University of Pennsylvania, Philadelphia]

Biophysical Journal. **107**, 1829-1840, 2014.

Contractile forces exerted on the surrounding extracellular matrix (ECM) lead to the alignment and stretching of constituent fibers within the vicinity of cells. As a consequence, the matrix reorganizes to form thick bundles of aligned fibers that enable force transmission over distances larger than the size of the cells. Contractile force-mediated remodeling of ECM fibers has bearing on a number of physiologic and pathophysiologic phenomena. In this work, we present a computational model to capture cell-mediated remodeling within fibrous matrices using finite element-based discrete fiber network simulations.

Understanding Nucleotide-Regulated FtsZ Filament Dynamics and the Monomer Assembly Switch with Large-Scale Atomistic Simulations

Erney Ramírez-Aportela, José Ramón López-Blanco, José Manuel Andreu, Pablo Chacón [Instituto de Química-Física Rocasolano]

Biophysical Journal. **107**, 2164-2176, 2014.

Bacterial cytoskeletal protein FtsZ assembles in a head-to-tail manner, forming dynamic filaments that are essential for cell division. Here, we study their dynamics using unbiased atomistic molecular simulations from representative filament crystal structures. In agreement with experimental data, we find different filament curvatures that are supported by a nucleotide-regulated hinge motion between consecutive FtsZ monomers. Whereas GTP-FtsZ filaments bend and twist in a preferred orientation, thereby burying the nucleotide, the differently curved GDP-FtsZ filaments exhibit a heterogeneous distribution of open and closed interfaces between monomers.

Kinesin-5 Allosteric Inhibitors Uncouple the Dynamics of Nucleotide, Microtubule, and Neck-Linker Binding Sites

Guido Scarabelli, Barry J. Grant [University of Michigan, Ann Arbor]

Biophysical Journal. **107**, 2204-2213, 2014.

Kinesin motor domains couple cycles of ATP hydrolysis to cycles of microtubule binding and conformational changes that result in directional force and movement on microtubules. The general principles of this mechanochemical coupling have been established; however, fundamental atomistic details of the underlying allosteric mechanisms remain unknown. Here, we combine unbiased molecular-dynamics simulations, bioinformatics analysis, and mutational studies to elucidate the structural dynamic effects of nucleotide turnover and allosteric inhibition of the kinesin-5 motor.

Protein Dynamics (Cont'd)

A molecular simulation study of the protection of insulin bioactive structure by trehalose

Daixi Li [University of Shanghai for Science and Technology], Li Liu, Huaxing Yu, Zhen Zhai, Yan Zhang, Baisong Guo, Chunsheng Yang, Baolin Liu

J. Mol.Mod., **20**, 2496, 2014.

Biopharmaceuticals are proteins with a crucial role in the treatment of many diseases. However, these protein medicines are often thermally labile and therefore unsuitable for long-term application and storage, as they tend to lose their activity under ambient conditions. Desiccation is one approach to improving protein stability, but the drying process itself can cause irreversible damage. In the current study, insulin was chosen as an example of a thermally sensitive biopharmaceutical to investigate whether the disaccharide, trehalose, can prevent loss of structural integrity due to drying. The experiment was performed using replica exchange molecular simulation and Gromacs software with a Gromos96 (53a6) force field.

Rapid Computational Prediction of Thermostabilizing Mutations for G Protein-Coupled Receptors

Supriyo Bhattacharya, Sangbae Lee, Reinhard Grisshammer, Christopher G. Tate, and Nagarajan Vaidehi [Beckman Research Institute of the City of Hope]

J. Chem. Theor. and Comp., **10**, 5149–5160, 2014.

G protein-coupled receptors (GPCRs) are highly dynamic and often denature when extracted in detergents. Deriving thermostable mutants has been a successful strategy to stabilize GPCRs in detergents, but this process is experimentally tedious. We have developed a computational method to predict the position of the thermostabilizing mutations for a given GPCR sequence. We have validated the method against experimentally measured thermostability data for single mutants of the β 1-adrenergic receptor (β 1AR), adenosine A2A receptor (A2AR) and neurotensin receptor 1 (NTSR1). To make these predictions we started from homology models of these receptors of varying accuracies and generated an ensemble of conformations by sampling the rigid body degrees of freedom of transmembrane helices.

Analysis of Factors Influencing Hydration Site Prediction Based on Molecular Dynamics Simulations

Ying Yang, Bingjie Hu, and Markus A. Lill [College of Pharmacy, Purdue University]

J.Chem. Infor. and Mod. **54**, 2987–2995, 2014.

Water contributes significantly to the binding of small molecules to proteins in biochemical systems. Molecular dynamics (MD) simulation based programs such as WaterMap and WATsite have been used to probe the locations and thermodynamic properties of hydration sites at the surface or in the binding site of proteins generating important information for structure-based drug design. However, questions associated with the influence of the simulation protocol on hydration site analysis remain. In this study, we use WATsite to investigate the influence of factors such as simulation length and variations in initial protein conformations on hydration site prediction.

Protein Dynamics (Cont'd)

Environmental Effect on Surface Immobilized Biological Molecules

Zunliang Wang, Xiaofeng Han, Nongyue He, Zhan Chen, and Charles L. Brooks, III [University of Michigan]

J. Phys. Chem. B., **118**, 12176–12185, 2014.

Our recent sum frequency generation (SFG) vibrational spectroscopic experiment (*J. Phys. Chem. B* 2014, 118, 2904–2912) showed that immobilized antimicrobial peptide cecropin P1 (cCP1) on a self-assembled monolayer (SAM) surface via N-terminus exhibited significantly different conformational and/or orientational behaviors when exposed to pure water vs a 50% (v/v) 2,2,2-trifluoroethanol (TFE)/water mixture. Here, MD simulations were performed on the immobilized cCP1 on a SAM surface via N-terminus while in contact with a 50% (v/v) TFE/water mixture to further investigate the effects of environment (water vs TFE/water mixture) on the interfacial structure and orientation of immobilized peptide.

Infinitely Dilute Partial Molar Properties of Proteins from Computer Simulation

Elizabeth A. Ploetz and Paul E. Smith [Kansas State University]

J. Phys. Chem. B., **118**, 12844–12854, 2014.

A detailed understanding of temperature and pressure effects on an infinitely dilute protein's conformational equilibrium requires knowledge of the corresponding infinitely dilute partial molar properties. Established molecular dynamics methodologies generally have not provided a way to calculate these properties without either a loss of thermodynamic rigor, the introduction of nonunique parameters, or a loss of information about which solute conformations specifically contributed to the output values. Here we implement a simple method that is thermodynamically rigorous and possesses none of the above disadvantages, and we report on the method's feasibility and computational demands.

Molecular dynamics of the structural changes of helical peptides induced by pressure

Yoshiharu Mori and Hisashi Okumura [Institute for Molecular Science, Okazaki]

Proteins: Stru. Fun. & Bioinf., **82**, 2970–2981, 2014.

An AK16 peptide and a C-peptide analog are experimentally known to form more helical structures under high-pressure conditions than those at atmospheric pressure, even though most proteins usually unfold at high pressure. To understand the pressure-induced structural changes of the two peptides, molecular dynamics simulations with the simulated tempering method for the isobaric-isothermal ensemble were performed in a wide pressure range from 0.1 MPa to 1.4 GPa. We found that the fraction of the folded state decreases once and then increases with increasing pressure for both peptides.

Protein Dynamics (Cont'd)

Dual effects of familial Alzheimer's disease mutations (D7H, D7N, and H6R) on amyloid β peptide: Correlation dynamics and zinc binding

Liang Xu [Dalian University of Technology], Yonggang Chen and Xiaojuan Wang

Proteins: Stru. Fun. & Bioinf., **82**, 3286–3297, 2014.

Although the N-terminal region of Amyloid β ($A\beta$) peptides plays dual roles as metal-coordinating sites and conformational modulator, few studies have been performed to explore the effects of mutations at this region on the overall conformational ensemble of $A\beta$ and the binding propensity of metal ions. In this work, we focus on how three familial Alzheimer's disease mutations (D7H, D7N, and H6R) alter the structural characteristics and thermodynamic stabilities of $A\beta_{42}$ using molecular dynamics simulations. We observe that each mutation displays increased β -sheet structures in both N and C termini.

Free Energy Calculations

Efficient calculation of relative binding free energies by umbrella sampling perturbation

Fabian Zeller and Martin Zacharias [Technische Universität München]

J. Comp. Chem., **35**, 2256–2262, 2014.

An important task of biomolecular simulation is the calculation of relative binding free energies upon chemical modification of partner molecules in a biomolecular complex. The potential of mean force (PMF) along a reaction coordinate for association or dissociation of the complex can be used to estimate binding affinities. A free energy perturbation approach, termed umbrella sampling (US) perturbation, has been designed that allows an efficient calculation of the change of the PMF upon modification of a binding partner based on the trajectories obtained for the wild type reference complex.

Molecular Simulations of the Pairwise Interaction of Monoclonal Antibodies

Mauro Lapelosa, Thomas W. Patapoff, and Isidro E. Zarraga [Genentech Inc., member of Roche]

J. Phys. Chem. B., **118**, 13132–13141, 2014.

Molecular simulations are employed to compute the free energy of pairwise monoclonal antibodies (mAbs) association using a conformational sampling algorithm with a scoring function. The work reported here is aimed at investigating the mAb–mAb association driven by weak interactions with a computational method capable of predicting experimental observations of low binding affinity. The simulations are able to explore the free energy landscape. A steric interaction component, electrostatic interactions, and a nonpolar component of the free energy form the energy scoring function.

Ligand Binding/Docking

Structure-Based Virtual Screening of the Nociceptin Receptor: Hybrid Docking and Shape-Based Approaches for Improved Hit Identification

Pankaj R. Daga, Willma E. Polgar, and Nurulain T. Zaveri [Astraea Therapeutics]

J.Chem. Infor. and Mod. **54**, 2732–2743, 2014.

The antagonist-bound crystal structure of the nociceptin receptor (NOP), from the opioid receptor family, was recently reported along with those of the other opioid receptors bound to opioid antagonists. We recently reported the first homology model of the ‘active-state’ of the NOP receptor, which when docked with ‘agonist’ ligands showed differences in the TM helices and residues, consistent with GPCR activation after agonist binding. In this study, we explored the use of the active-state NOP homology model for structure-based virtual screening to discover NOP ligands containing new chemical scaffolds.

A Large-Scale Test of Free-Energy Simulation Estimates of Protein–Ligand Binding Affinities

Paulius Mikulskis, Samuel Genheden, and Ulf Ryde [Lund University]

J.Chem. Infor. and Mod. **54**, 2794–2806, 2014.

We have performed a large-scale test of alchemical perturbation calculations with the Bennett acceptance-ratio (BAR) approach to estimate relative affinities for the binding of 107 ligands to 10 different proteins. Employing 20-Å truncated spherical systems and only one intermediate state in the perturbations, we obtain an error of less than 4 kJ/mol for 54% of the studied relative affinities and a precision of 0.5 kJ/mol on average. However, only four of the proteins gave acceptable errors, correlations, and rankings.

Structure-Based Drug Design of Diphenyl α -Aminoalkylphosphonates as Prostate-Specific Antigen Antagonists

Arben Kojtari, Vishal Shah, Jacob S. Babinec, Catherine Yang, and Hai-Feng Ji [Drexel University]

J.Chem. Infor. and Mod. **54**, 2967–2979, 2014.

Here, we describe the mechanism of diphenyl α -aminoalkylphosphonate ester derivatives as potent inhibitors of prostate-specific antigen (PSA), a likely protease responsible for the advancement of prostate tumor progression. The AutoDock 4.2 molecular docking suite was utilized to model covalent and noncovalent binding of this class of inhibitors to predict crystallographic poses and compare experimental IC₅₀ dose–response curves and in silico potencies for providing future more specific rational drug design.

Extensive Consensus Docking Evaluation for Ligand Pose Prediction and Virtual Screening Studies

Tiziano Tuccinardi [University of Pisa], Giulio Poli, Veronica Romboli, Antonio Giordano, and Adriano Martinelli

J.Chem. Infor. and Mod. **54**, 2980–2986, 2014.

Molecular docking strategies are one of the most widely used techniques for predicting the binding mode of a ligand and for obtaining new hits in virtual screening studies. In order to improve the accuracy of this approach, we tested the reliability of applying a consensus docking protocol by combining ten different docking procedures. The analysis was carried out in terms of consensus cross-docking and by using an enriched database. The results highlight that from a qualitative point of view consensus docking is able to predict the ligand binding pose better than the single docking programs and is also able to give hints concerning the reliability of the docking pose.

Ligand Binding / Docking (Cont'd)

Disorder in Cholesterol-Binding Functionality of CRAC Peptides: A Molecular Dynamics Study

Cayla M. Miller, Angela C. Brown, and Jeetain Mittal
[Lehigh University, Bethlehem]

J. Phys. Chem. B., **118**, 13169–13174, 2014.

The cholesterol recognition/interaction amino acid consensus (CRAC) motif is a primary structure pattern used to identify regions that may be responsible for preferential cholesterol binding in many proteins. The leukotoxin LtxA, which is produced by a pathogenic bacterium, contains two CRAC sequences, only one of which is responsible for cholesterol binding, and the binding is required for cytotoxicity. This study uses molecular dynamics simulations to identify structural characteristics and specific interactions of the two LtxA CRAC peptides with both pure phospholipid and binary cholesterol–phospholipid bilayers.

Talin-driven inside-out activation mechanism of platelet $\alpha\text{IIb}\beta 3$ integrin probed by multimicrosecond, all-atom molecular dynamics simulations

Davide Provasi, Ana Negri, Barry S. Collier and Marta Filizola [Icahn School of Medicine at Mount Sinai]

Proteins: Stru. Fun. & Bioinf., **82**, 3231–3240, 2014.

Platelet aggregation is the consequence of the binding of extracellular bivalent ligands such as fibrinogen and von Willebrand factor to the high affinity, active state of integrin $\alpha\text{IIb}\beta 3$. This state is achieved through a so-called “inside-out” mechanism characterized by the membrane-assisted formation of a complex between the F2 and F3 subdomains of intracellular protein talin and the integrin $\beta 3$ tail. Here, we present the results of multimicrosecond, all-atom molecular dynamics simulations carried on the complete transmembrane (TM) and C-terminal (CT) domains of $\alpha\text{IIb}\beta 3$ integrin in an explicit lipid-water environment, and in the presence or absence of the talin-1 F2 and F3 subdomains.

Enzyme Catalysis

Conformational State Distributions and Catalytically Relevant Dynamics of a Hinge-Bending Enzyme Studied by Single-Molecule FRET and a Coarse-Grained Simulation

Matteo Gabba, Simón Poblete, Tobias Rosenkranz, Alexandros Katranidis, Daryan Kempe, Tina Züchner, Roland G. Winkler, Gerhard Gompper, Jörg Fitter [Institute of Complex Systems (ICS-5) Molecular Biophysics]

Biophysical Journal. **107**, 1913–1923, 2014.

Over the last few decades, a view has emerged showing that multidomain enzymes are biological machines evolved to harness stochastic kicks of solvent particles into highly directional functional motions. These intrinsic motions are structurally encoded, and Nature makes use of them to catalyze chemical reactions by means of ligand-induced conformational changes and states redistribution. Such mechanisms align reactive groups for efficient chemistry and stabilize conformers most proficient for catalysis. By combining single-molecule Förster resonance energy transfer measurements with normal mode analysis and coarse-grained mesoscopic simulations, we obtained results for a hinge-bending enzyme, namely phosphoglycerate kinase (PGK), which support and extend these ideas.

Enzyme Catalysis (Cont'd)

Bridging the Missing Link between Structure and Fidelity of the RNA-Dependent RNA Polymerase from Poliovirus through Free Energy Simulations

Hujun Shen and Guohui Li [Dalian Institute of Chemical Physics]

J. Chem. Theor. and Comp., **10**, 5195–5205, 2014.

RNA-dependent RNA polymerases (RdRps) are enzymes catalyzing RNA replication from a RNA template. Active-site closure in RdRps, normally induced by correct nucleotide triphosphate (NTP) binding, is a prerequisite for the cycle of nucleotide incorporation. So, a complete understanding of polymerase function (in particular polymerase fidelity) of a RdRp requires more complete knowledge of active-site closure in the RdRp. In this work, based on solved crystal structures, we have built different models for the RNA-dependent RNA polymerase from poliovirus (termed PV 3Dpol).

Computational Investigation of the Initial Two-Electron, Two-Proton Steps in the Reaction Mechanism of Hydroxylamine Oxidoreductase

Amr A. A. Attia and Radu Silaghi-Dumitrescu [Babes-Bolyai University]

J. Phys. Chem. B., **118**, 12140–12145, 2014.

Reported here is a computational study based on density functional theory that presents the first attempt to investigate the 2-electron 2-proton reaction of Fe(III)–H₂NOH to Fe(III)–HNO in the catalytic cycle of hydroxylamine oxidoreductase—a multiheme-containing enzyme that catalyzes the conversion of hydroxylamine (HA) to nitrite in nitrifying bacteria. Two subsequent protonation events are proposed to initiate the process, of which the second is suggested to be concerted with a one-electron oxidation.

Simulating the Catalytic Effect of a Designed Mononuclear Zinc Metalloenzyme that Catalyzes the Hydrolysis of Phosphate Triesters

Manoj Kumar Singh, Zhen T. Chu, and Arie Warshel [University of Southern California]

J. Phys. Chem. B., **118**, 12146–12152, 2014.

One of the greatest challenges in biotechnology and in biochemistry is the ability to design efficient enzymes. In fact, such an ability would be one of the most convincing manifestations of a full understanding of the origin of enzyme catalysis. In this work we examine the ability of the empirical valence bond (EVB) to reproduce the results of directed evolution improvements of the catalysis of diethyl 7-hydroxycoumarinyl by a designed mononuclear zinc metalloenzyme. Encouragingly, our study reproduced the catalytic effect obtained by directed evolution and offers a good start for further studies of this system.

pH-REMD Simulations Indicate That the Catalytic Aspartates of HIV-1 Protease Exist Primarily in a Monoprotonated State

T. Dwight McGee, Jr., Jesse Edwards, and Adrian E. Roitberg [University of Florida]

J. Phys. Chem. B., **118**, 12577–12585, 2014.

The protonation state of the catalytic aspartates of HIV-1 protease (HIVPR) is atypical and as a result is the subject of much debate. Modeling of the correct protonation state of the aspartates is vital in computational drug design. Using pH replica-exchange molecular dynamics, we simulated the apo and bound forms of HIV-1 protease with 12 different protease inhibitors to investigate the pK_a of not only the catalytic dyad but also the other titrating residues in HIVPR. The results obtained from these simulations are compared to experiment where possible.

Enzyme Catalysis (Cont'd)

Solution NMR studies reveal no global flexibility in the catalytic domain of CDC25B

George Lund and Tomasz Cierpicki [University of Michigan]

Proteins: Stru. Fun. & Bioinf., **82**, 2889–2895, 2014.

The CDC25B phosphatase is a critical regulator of the cell cycle and has been validated as an important therapeutic target in cancer. Previous studies using molecular dynamics simulations have concluded that the catalytic domain of CDC25B may experience a significant degree of dynamics or be partially disordered in solution, a finding that has a pronounced impact on the structure-based development of CDC25B inhibitors. We have probed the backbone dynamics of the CDC25B catalytic domain in solution using NMR relaxation experiments and found that the core of the protein is relatively rigid and does not experience any large-scale dynamics over a broad range of time scales.

Structural insights into substrate and coenzyme preference by SDR family protein Gox2253 from *Gluconobacter oxydans*

Bo Yin, Dongbing Cui, Lujia Zhang, Shuiqin Jiang, Satoru Machida, Y. Adam Yuan and Dongzhi Wei [East China University of Science and Technology]

Proteins: Stru. Fun. & Bioinf., **82**, 2925–2935, 2014.

Gox2253 from *Gluconobacter oxydans* belongs to the short-chain dehydrogenases/reductases family, and catalyzes the reduction of heptanal, octanal, nonanal, and decanal with NADPH. To develop a robust working platform to engineer novel *G. oxydans* oxidoreductases with designed coenzyme preference, we adopted a structure based rational design strategy using computational predictions that considers the number of hydrogen bonds formed between enzyme and docked coenzyme. We report the crystal structure of Gox2253 at 2.6 Å resolution, ternary models of Gox2253 mutants in complex with NADH/short-chain aldehydes, and propose a structural mechanism of substrate selection.

Empirical valence bond simulations of the hydride transfer step in the monoamine oxidase B catalyzed metabolism of dopamine

Matej Repič, Robert Vianello, Miha Purg, Fernanda Duarte, Paul Bauer, Shina C. L. Kamerlin and Janez Mavri [National Institute of Chemistry, Ljubljana]

Proteins: Stru. Fun. & Bioinf., **82**, 3347–3355, 2014.

Monoamine oxidases (MAOs) A and B are flavoenzymes responsible for the metabolism of biogenic amines such as dopamine, serotonin and noradrenaline. We present a complete study of the rate-limiting step of dopamine degradation by MAO B, which consists in the hydride transfer from the methylene group of the substrate to the flavin moiety of the FAD prosthetic group. This article builds on our previous quantum chemical study of the same reaction using a cluster model but now considering the full dimensionality of the hydrated enzyme with extensive configurational sampling.

Physics-based enzyme design: Predicting binding affinity and catalytic activity

Sarah Sirin, David A. Pearlman and Woody Sherman [Schrödinger, Inc., New York]

Proteins: Stru. Fun. & Bioinf., **82**, 3397–3409, 2014.

Computational enzyme design is an emerging field that has yielded promising success stories, but where numerous challenges remain. Accurate methods to rapidly evaluate possible enzyme design variants could provide significant value when combined with experimental efforts by reducing the number of variants needed to be synthesized and speeding the time to reach the desired endpoint of the design. To that end, extending our computational methods to model the fundamental physical-chemical principles that regulate activity in a protocol that is automated and accessible to a broad population of enzyme design researchers is essential.

Protein-Protein Interactions

Protein-Protein Interactome

Docking: From Interaction to

The protein-protein docking problem is one of the focal points of activity in computational biophysics and structural biology. The three-dimensional structure of a protein-protein complex, generally, is more difficult to determine experimentally than the structure of an individual protein. Docking offers tools for fundamental studies of protein interactions and provides a structural basis for drug design. Protein-protein docking is the prediction of the structure of the complex, given the structures of the individual proteins.

Ilya A. Vakser [The University of Kansas, Lawrence]

Biophysical Journal. **107**, 1785-1793, 2014.

Balanced Protein–Water Interactions Improve Properties of Disordered Proteins and Non-Specific Protein Association

Some frequently encountered deficiencies in all-atom molecular simulations, such as nonspecific protein–protein interactions being too strong, and unfolded or disordered states being too collapsed, suggest that proteins are insufficiently well solvated in simulations using current state-of-the-art force fields. To address these issues, we make the simplest possible change, by modifying the short-range protein–water pair interactions, and leaving all the water–water and protein–protein parameters unchanged.

Robert B. Best, Wenwei Zheng, and Jeetain Mittal [Lehigh University, Bethlehem]

J. Chem. Theor. and Comp, **10**, 5113–5124, 2014.

Membrane Proteins and Lipid Peptide Interactions

Atomistic Molecular-Dynamics Simulations Enable Prediction of the Arginine Permeation Pathway through OccD1/OprD from *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram-negative bacterium that does not contain large, nonspecific porins in its outer membrane. Consequently, the outer membrane is highly impermeable to polar solutes and serves as a barrier against the penetration of antimicrobial agents. This is one of the reasons why such bacteria are intrinsically resistant to antibiotics. Polar molecules that permeate across the outer membrane do so through substrate-specific channels proteins. To design antibiotics that target substrate-channel proteins, it is essential to first identify the permeation pathways of their natural substrates.

Jamie Parkin, Syma Khalid [University of Southampton, Southampton]

Biophysical Journal. **107**, 1853-1861, 2014.

Beware of Machine Learning-Based Scoring Functions—On the Danger of Developing Black Boxes

Training machine learning algorithms with protein–ligand descriptors has recently gained considerable attention to predict binding constants from atomic coordinates. Starting from a series of recent reports stating the advantages of this approach over empirical scoring functions, we could indeed reproduce the claimed superiority of Random Forest and Support Vector Machine-based scoring functions to predict experimental binding constants from protein–ligand X-ray structures of the PDBBind dataset.

Joffrey Gabel, J  r  my Desaphy, and Didier Rognan [CNRS-Universit   de Strasbourg]

J.Chem. Infor. and Mod. **54**, 2807–2815, 2014.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Peptides with the Same Composition, Hydrophobicity, and Hydrophobic Moment Bind to Phospholipid Bilayers with Different Affinities

Melissa A. Cherry, Sarah K. Higgins, Hilary Melroy, Hee-Seung Lee, and Antje Pokorny [University of North Carolina Wilmington]

J. Phys. Chem. B., **118**, 12462–12470, 2014.

We investigated the dependence of membrane binding on amino acid sequence for a series of amphipathic peptides derived from δ -lysin. δ -Lysin is a 26 amino acid, N-terminally formylated, hemolytic peptide that forms an amphipathic α -helix bound at membrane–water interfaces. A shortened peptide, lysette, was derived from δ -lysin by deletion of the four N-terminal amino acid residues. Five variants of lysette were synthesized by altering the amino acid sequence such that the overall hydrophobic moment remained essentially the same for all peptides. Peptide–lipid equilibrium dissociation constants and helicities of peptides bound to zwitterionic lipid vesicles were determined by stopped-flow fluorescence and circular dichroism.

Local Pressure Changes in Lipid Bilayers Due to Adsorption of Melittin and Magainin-h2 Antimicrobial Peptides: Results from Computer Simulations

Ardeshir Goliaei, Kolattukudy P. Santo, and Max L. Berkowitz [University of North Carolina at Chapel Hill]

J. Phys. Chem. B., **118**, 12673–12679, 2014.

We performed a series of coarse-grained computer simulations in order to study how the placement of melittin and magainin-h2 antimicrobial peptides on the surface of the bilayer changes the local pressure profiles in the bilayer. The simulations were done using the NPT ensemble when the total stress on the bilayer was zero and also using the NP_zAT ensemble, with a nonzero total stress. In the NPT ensemble, although the total stress was zero, each leaflet of the bilayer experienced a nonzero stress, and the stresses are equal by magnitude, but opposite in their direction.

Exploring the Local Elastic Properties of Bilayer Membranes Using Molecular Dynamics Simulations

Gilles Pieffet, Alonso Botero, Günther H. Peters, Manu Forero-Shelton, and Chad Leidy [Universidad de los Andes]

J. Phys. Chem. B., **118**, 12883–12891, 2014.

Membrane mechanical elastic properties regulate a variety of cellular processes involving local membrane deformation, such as ion channel function and vesicle fusion. In this work, we used molecular dynamics simulations to estimate the local elastic properties of a membrane. For this, we calculated the energy needed to extract a DOPE lipid molecule, modified with a linker chain, from a POPC bilayer membrane using the umbrella sampling technique. Although the extraction energy entails several contributions related not only to elastic deformation but also to solvation, careful analysis of the potential of mean force (PMF) allowed us to dissect the elastic contribution.

Flip-Flop of Oleic Acid in a Phospholipid Membrane: Rate and Mechanism

Chenyu Wei and Andrew Pohorille [NASA Ames Research Center]

J. Phys. Chem. B., **118**, 12919–12926, 2014.

Flip-flop of protonated oleic acid molecules dissolved at two different concentrations in membranes made of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine is studied with the aid of MD simulations at a time scale of several microseconds. Direct, single-molecule flip-flop events are observed at this time scale, and the flip-flop rate is estimated at $0.2\text{--}0.3\ \mu\text{s}^{-1}$. As oleic acid molecules move toward the center of the bilayer during flip-flop, they undergo gradual, correlated translational, and rotational motion. Rare, double-flipping events of two hydrogen-bonded oleic acid molecules are also observed.

Membrane Proteins and Lipid Peptide Interactions (Cont'd)

Structures, Dynamics, and Water Permeation Free Energy across Bilayers of Lipid A and Its Analog Studied with Molecular Dynamics Simulation

Tao Wei [Lamar University, Beaumont], Tiefan Huang, Baofu Qiao, Mo Zhang, Heng Ma, and Lin Zhang

J. Phys. Chem. B., **118**, 13202–13209, 2014.

Fundamental studies of the supramolecular layer structures, dynamics and water permeation free energy of hexa-acyl-chain Lipid A and its analogue of tetra-acyl chains would be useful for polymer membranes design for endotoxin removal in water treatment, drug delivery and other biotechnologies. In this work, we studied their supramolecular bilayer by using molecular dynamics simulations and efficient free energy computations. Our simulation accuracy was verified by the agreement between the bilayer structural properties (structure factor, bilayer thickness, and the area per lipid) and lateral diffusion coefficient in our simulation and experimental measurements.

The N-terminal of annexin A1 as a secondary membrane binding site: A molecular dynamics study

Matthew P. Donohue, Libero J. Bartolotti and Yumin Li [East Carolina University]

Proteins: Stru. Fun. & Bioinf., **82**, 2936–2942, 2014.

Annexin A1 has been shown to cause membrane aggregation and fusion, yet the mechanism of these activities is not clearly understood. In this work, molecular dynamics simulations were performed on monomeric annexin A1 positioned between two negatively charged monolayers using AMBER's all atom force field to gain insight into the mechanism of fusion. Each phospholipid monolayer was made up of 180 DOPC molecules and 45 DOPG molecules to achieve a 4:1 ratio. The space between the two monolayers was explicitly solvated using TIP3P waters in a rectilinear box.

Terminal sialic acids on CD44 N-glycans can block hyaluronan binding by forming competing intramolecular contacts with arginine sidechains

Christina E. Faller and Olgun Guvench [University of New England College of Pharmacy]

Proteins: Stru. Fun. & Bioinf., **82**, 3079–3089, 2014.

Specific sugar residues and their linkages form the basis of molecular recognition for interactions of glycoproteins with other biomolecules. Seemingly small changes, like the addition of a single monosaccharide in the covalently attached glycan component of glycoproteins, can greatly affect these interactions. For instance, the sialic acid capping of glycans affects protein-ligand binding involved in cell–cell and cell–matrix interactions. CD44 is a single-pass transmembrane glycoprotein whose binding with its carbohydrate ligand hyaluronan (HA), an extracellular matrix component, mediates processes such as leukocyte homing, cell adhesion, and tumor metastasis.

Lipid-associated aggregate formation of superoxide dismutase-1 is initiated by membrane-targeting loops

Choon-Peng Chng [A*STAR (Agency for Science, Technology and Research)] and Richard W. Strange

Proteins: Stru. Fun. & Bioinf., **82**, 3194–3209, 2014.

Copper-Zinc superoxide dismutase 1 (SOD1) is a homodimeric enzyme that protects cells from oxidative damage. The cytotoxicity of demetallated or apo-SOD1 aggregates may be due to their ability to cause defects within cell membranes by co-aggregating with phospholipids. SOD1 monomers may associate with the inner cell membrane to receive copper ions from membrane-bound copper chaperones. But how apo-SOD1 interacts with lipids is unclear. We have used atomistic MD simulations to reveal that flexible electrostatic and zinc-binding loops in apo-SOD1 dimers play a critical role in the binding of 1-octanol clusters and phospholipid bilayer, without any significant unfolding of the protein.

Protein Folding

Unbinding and unfolding of adhesion protein complexes through stretching: Interplay between shear and tensile mechanical clamps

Bartosz Różycki [Polish Academy of Sciences], Łukasz Mioduszeński and Marek Cieplak

Proteins: Stru. Fun. & Bioinf., **82**, 3144–3153, 2014.

Using coarse-grained molecular dynamics simulations, we analyze mechanically induced dissociation and unfolding of the protein complex CD48-2B4. This heterodimer is an indispensable component of the immunological system: 2B4 is a receptor on natural killer cells whereas CD48 is expressed on surfaces of various immune cells. So far, its mechanostability has not been assessed either experimentally or theoretically. We find that the dissociation processes strongly depend on the direction of pulling and may take place in several pathways. Interestingly, the CD48-2B4 interface can be divided into three distinct patches that act as units when resisting the pulling forces.

Protein-Nucleic acid Interactions

Contribution of phenylalanine side chain intercalation to the TATA-box binding protein–DNA interaction: molecular dynamics and dispersion-corrected density functional theory studies

Manas Mondal, Sanchita Mukherjee, Dhananjay Bhattacharyya [Saha Institute of Nuclear Physics]

J. Mol.Mod., **20**, 2499, 2014.

Deformation of DNA takes place quite often due to binding of small molecules or proteins with DNA. Such deformation is significant due to minor groove binding and, besides electrostatic interactions, other non-covalent interactions may also play an important role in generating such deformation. TATA-box binding protein (TBP) binds to the minor groove of DNA at the TATA box sequence, producing a large-scale deformation in DNA and initiating transcription. In order to observe the interactions of protein residues with DNA in the minor groove that produce the deformation in the DNA structure, we carried out molecular dynamics simulations of the TBP–DNA system.

Truncated Variants of the GCN4 Transcription Activator Protein Bind DNA with Dramatically Different Dynamical Motifs

Danielle M. McHarris and Daniel A. Barr [Utica College]

J.Chem. Infor. and Mod. **54**, 2869–2875, 2014.

The yeast protein GCN4 is a transcriptional activator in the basic leucine zipper (bZip) family, whose distinguishing feature is the “chopstick-like” homodimer of alpha helices formed at the DNA-binding interface. While experiments have shown that truncated versions of the protein retain biologically relevant DNA-binding affinity, we present the results of a computational study revealing that these variants show a wide variety of dynamical modes in their interaction with the target DNA sequence. We have performed all-atom molecular dynamics simulations of the full-length GCN4 protein as well as three truncated variants; our data indicate that the truncated mutants show dramatically different correlation patterns.

Protein - Nucleic Acid Interactions (Cont'd)

Specific Recognition Mechanism between RNA and the KH3 Domain of Nova-2 Protein

Qingfen Yu, Wei Ye, Cheng Jiang, Ray Luo, and Hai-Feng Chen [Shanghai Jiaotong University]

J. Phys. Chem. B., **118**, 12426–12434, 2014.

The KH3 domain of Nova-2 protein can precisely recognize the sequence-specific target RNA of human glycine receptor $\alpha 2$. However, the recognition mechanism between the protein and its target RNA is still hotly debated. In this study, molecular dynamic simulations in explicit solvent were utilized to understand the recognition mechanism. The structural analysis and the Kolmogorov–Smirnov P-test statistics reveal that the KH3 domain might obey a conformational selection mechanism upon RNA binding. However, the induced fit mechanism could not be completely ruled out. Unfolding kinetics indicates that the folding of RNA and KH3 happens first and then the binding between RNA and KH3 follows.

DNA Recognition Process of the Lactose Repressor Protein Studied via Metadynamics and Umbrella Sampling Simulations

Simone Furini [University of Siena] and Carmen Domene

J. Phys. Chem. B., **118**, 13059–13065, 2014.

The lactose repressor, LacI, finds its DNA target sites via a process that is faster than what it is expected from a diffusion-driven mechanism. This is possible thanks to nonspecific binding of LacI to DNA, followed by diffusion along the DNA molecule. The diffusion of the protein along DNA might lead to a fast-searching mechanism only if LacI binds with comparable strength to different nonspecific sequences and if, in addition, the value of the binding energy remarkably decreases in the presence of a binding site. The first condition would be favored by loose interactions with the base edges, while the second would take advantage from the opposite situation.

Nucleic Acids

Enhanced sampling simulations of DNA step parameters

Aleksandra Karolak and Arjan van der Vaart [University of South Florida]

J. Comp. Chem., **35**, 2297–2304, 2014.

A novel approach for the selection of step parameters as reaction coordinates in enhanced sampling simulations of DNA is presented. The method uses three atoms per base and does not require coordinate overlays or idealized base pairs. This allowed for a highly efficient implementation of the calculation of all step parameters and their Cartesian derivatives in molecular dynamics simulations. Good correlation between the calculated and actual twist, roll, tilt, shift, and slide parameters is obtained, while the correlation with rise is modest.

Nucleic Acids (Cont'd)

Understanding the recognition mechanisms of Z α domain of human editing enzyme ADAR1 (hZ α _{ADAR1}) and various Z-DNAs from molecular dynamics simulation

Qianqian Wang, Lanlan Li, Xiaoting Wang, Huanxiang Liu [Lanzhou University], Xiaojun Yao

J. Mol.Mod., **20**, 2500, 2014.

The Z-DNA-binding domain of human double-stranded RNA adenosine deaminase I (hZ α _{ADAR1}) can specifically recognize the left-handed Z-DNA which preferentially occurs at alternating purine-pyrimidine repeats, especially the CG-repeats. The interactions of hZ α _{ADAR1} and Z-DNAs in different sequence contexts can affect many important biological functions including gene regulation and chromatin remodeling. Here, based on the recently determined crystal structures of three representative non-CG-repeat Z-DNAs (d(CACGTG)₂, d(CGTACG)₂ and d(CGGCCG)₂) in complex with hZ α _{ADAR1}, 40 ns molecular dynamics simulation together with binding free energy calculation were performed for each system.

A Simple and Fast Approach for Predicting ¹H and ¹³C Chemical Shifts: Toward Chemical Shift-Guided Simulations of RNA

Aaron T. Frank, Sean M. Law, and Charles L. Brooks, III [University of Michigan]

J. Phys. Chem. B., **118**, 12168–12175, 2014.

We introduce a simple and fast approach for predicting RNA chemical shifts from interatomic distances that performs with an accuracy similar to existing predictors and enables the first chemical shift-restrained simulations of RNA to be carried out. Our analysis demonstrates that the applied restraints can effectively guide conformational sampling toward regions of space that are more consistent with chemical shifts than the initial coordinates used for the simulations. As such, our approach should be widely applicable in mapping the conformational landscape of RNAs via chemical shift-guided molecular dynamics simulations.

Surfaces, Catalysts, and Materials Subjects

Protein modeling and molecular dynamics simulation of the two novel surfactant proteins SP-G and SP-H

Felix Rausch [Friedrich Alexander University Erlangen-Nuremberg], Martin Schicht, Lars Bräuer, Friedrich Paulsen, Wolfgang Brandt

J. Mol.Mod., **20**, 2513, 2014.

Surfactant proteins are well known from the human lung where they are responsible for the stability and flexibility of the pulmonary surfactant system. They are able to influence the surface tension of the gas–liquid interface specifically by directly interacting with single lipids. This work describes the generation of reliable protein structure models to support the experimental characterization of two novel putative surfactant proteins called SP-G and SP-H. The obtained protein models were complemented by predicted posttranslational modifications and placed in a lipid model system mimicking the pulmonary surface.

Surfaces, Catalysts and Material Subjects (Cont'd)

Molecular Dynamics Study of Surfactant-Like Peptide Based Nanostructures

Guilherme Colherinhas and Eudes Fileti [Universidade Federal de São Paulo]

J. Phys. Chem. B., **118**, 12215–12222, 2014.

Surfactant-like peptide (SLP) based nanostructures are investigated using all-atomistic molecular dynamics (MD) simulations. We report structure properties of nanostructures belonging to the A_NK peptide group. In particular, the mathematical models for the two A₃K membranes, A₆K nanotube, and A₉K nanorod were developed. Our MD simulation results are consistent with the experimental data, indicating that A₃K membranes are stable in two different configurations: (1) SLPs are tilted relative to the normal membrane plane; (2) SLPs are interdigitated. The former configuration is energetically more stable.

2. METHODOLOGY

Potentials and Parameters

Extension and validation of the GROMOS 53A6_{glyc} parameter set for glycoproteins

Laercio Pol-Fachin, Hugo Verli and Roberto D. Lins [Federal University of Pernambuco]

J. Comp. Chem., **35**, 2087–2095, 2014.

An extension of the GROMOS 53A6_{GLYC} force field for carbohydrates to encompass glycoprotein linkages is presented. The set includes new atomic charges and incorporates adequate torsional potential parameters for N-, S-, C-, P-, and O-glycosidic linkages, offering compatibility with the GROMOS force field family for proteins. Validation included the description of glycosidic linkage geometries between amino acid and monosaccharide residues, comparison of NMR-derived protein-carbohydrate and carbohydrate-carbohydrate nuclear overhauser effect (NOE) signals for glycoproteins and the effects of glycosylation on protein flexibility and dynamics.

Characteristics of protein residue-residue contacts and their application in contact prediction

Pawel P. Wozniak, Malgorzata Kotulska [Wroclaw University of Technology]

J. Mol.Mod., **20**, 2497, 2014.

Contact sites between amino acids characterize important structural features of a protein. We investigated characteristics of contact sites in a representative set of proteins and their relations between protein class or topology. For this purpose, we used a non-redundant set of 5872 protein domains, identically categorized by CATH and SCOP databases. The proteins represented alpha, beta, and alpha+beta classes. Contact maps of protein structures were obtained for a selected set of physical distances in the main backbone and separations in protein sequences. For each set a dependency between contact degree and distance parameters was quantified.

Potentials and Parameters (Cont'd)

A consistent force field parameter set for zwitterionic amino acid residues

Anselm H. C. Horn [Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU)]

J. Mol.Mod., **20**, 2478, 2014.

Isolated amino acids play an important role in biochemistry and are therefore an interesting object of study. Atomistic molecular dynamics (MD) simulations can provide a high-resolution picture of the dynamic features of these species, especially in their biological environment. Unfortunately, most standard force field packages lack libraries for isolated amino acids in their zwitterionic form. Here, we present such a parameter library derived from the widely used parm99SB set from the AMBER program package.

COFFDROP: A Coarse-Grained Nonbonded Force Field for Proteins Derived from All-Atom Explicit-Solvent Molecular Dynamics Simulations of Amino Acids

Casey T. Andrews and Adrian H. Elcock [University of Iowa, Iowa City]

J. Chem. Theor. and Comp., **10**, 5178–5194, 2014.

We describe the derivation of a set of bonded and nonbonded coarse-grained (CG) potential functions for use in implicit-solvent Brownian dynamics (BD) simulations of proteins derived from all-atom explicit-solvent molecular dynamics (MD) simulations of amino acids. Bonded potential functions were derived from 1 μ s MD simulations of each of the 20 canonical amino acids, with histidine modeled in both its protonated and neutral forms; nonbonded potential functions were derived from 1 μ s MD simulations of every possible pairing of the amino acids (231 different systems).

Macrocycle Conformational Sampling with MacroModel

K. Shawn Watts, Pranav Dalal, Andrew J. Tebben, Daniel L. Cheney, and John C. Shelley [Schrödinger, Inc.]

J.Chem. Infor. and Mod. **54**, 2680–2696, 2014.

Sampling low energy conformations of macrocycles is challenging due to the large size of many of these molecules and the constraints imposed by the macrocycle. We present a new conformational search method (implemented in MacroModel) that uses brief MD simulations followed by minimization and normal-mode search steps. The method was parametrized using a set of 100 macrocycles from the PDB and CSD. Possible origins for this and ideas for improving the performance on very large macrocycles are discussed.

Solvation Energy

A new set of atomic radii for accurate estimation of solvation free energy by Poisson–Boltzmann solvent model

Junya Yamagishi, Noriaki Okimoto [Quantitative Biology Center (QBiC)], Gentaro Morimoto and Makoto Taiji

J. Comp. Chem., **35**, 2132–2139, 2014.

The Poisson–Boltzmann implicit solvent (PB) is widely used to estimate the solvation free energies of biomolecules in molecular simulations. An optimized set of atomic radii (PB radii) is an important parameter for PB calculations, which determines the distribution of dielectric constants around the solute. We here present new PB radii for the AMBER protein force field to accurately reproduce the solvation free energies obtained from explicit solvent simulations. The presented PB radii were optimized using results from explicit solvent simulations of the large systems.

Molecular Dynamics

Proton Transfer in the K-Channel Analog of B-Type Cytochrome c Oxidase from *Thermus thermophilus*

Anna Lena Woelke, Anke Wagner, Gegham Galstyan, Tim Meyer, Ernst-Walter Knapp [Freie Universität Berlin, Berlin]

Biophysical Journal. **107**, 2177-2184, 2014.

A key enzyme in aerobic metabolism is cytochrome c oxidase (CcO), which catalyzes the reduction of molecular oxygen to water in the mitochondrial and bacterial membranes. The well-studied A-type CcO uses two different entry channels for protons: the D-channel for all pumped and two consumed protons, and the K-channel for the other two consumed protons. In contrast, the B-type CcO uses only a single proton input channel for all consumed and pumped protons. It has the same location as the A-type K-channel (and thus is named the K-channel analog) without sharing any significant sequence homology. In this study, we performed molecular-dynamics simulations and electrostatic calculations to characterize the K-channel analog in terms of its energetic requirements and functionalities.

Electron and Hydrogen Atom Transfers in the Hydride Carrier Protein EmoB

Natacha Gillet, Bernard Lévy, Vicent Moliner, Isabelle Demachy, and Aurélien de la Lande [Université Paris Sud]

J. Chem. Theor. and Comp, **10**, 5036–5046, 2014.

In this article, we investigate the mechanism of hydride transfer taking place within the EmoB protein of the *Mesorhizobium* species. The reaction involves the net transfer of one proton and two electrons from a reduced flavin mononucleotide (FMN) cofactor, which is anchored in the protein scaffold, to a diffusible oxidized FMN cofactor, both being held together by π -stacking interactions. To analyze the formal hydride transfer in terms of more elementary steps, electron transfer (ET), and hydrogen atom transfers (HAT), we employ a combination of classical molecular dynamics simulations and hybrid constrained Density Functional Theory/Molecular Mechanics (cDFT/MM) energy calculations to build the free energy profiles, for the ET before and after HAT occurs between the flavins.

Prediction of Compound Potency Changes in Matched Molecular Pairs Using Support Vector Regression

Antonio de la Vega de León and Jürgen Bajorath [Rheinische Friedrich-Wilhelms-Universität]

J.Chem. Infor. and Mod. **54**, 2654–2663, 2014.

Matched molecular pairs (MMPs) consist of pairs of compounds that are transformed into each other by a substructure exchange. If MMPs are formed by compounds sharing the same biological activity, they encode a potency change. If the potency difference between MMP compounds is very small, the substructure exchange (chemical transformation) encodes a bioisosteric replacement; if the difference is very large, the transformation encodes an activity cliff. For a given compound activity class, MMPs comprehensively capture existing structural relationships and represent a spectrum of potency changes for structurally analogous compounds. We have aimed to predict potency changes encoded by MMPs.

Molecular Dynamics (Cont'd)

Molecular Dynamics Simulation of Protein Crystal with Polarized Protein-Specific Force Field

Yongxiu Li, John Z. H. Zhang, and Ye Mei [East China Normal University]

J. Phys. Chem. B., **118**, 12326–12335, 2014.

Two 250 ns molecular simulations have been carried out to study the structure and dynamics of crystal toxin protein II from the scorpion *Androctonus australis Hector* employing the polarized protein-specific charge (PPC), as well as the standard AMBER99SB force field, to investigate the electrostatic polarization on the simulated crystal stability. Results show that under PPC, the monomers in unit cell as well as the lattice in supercell are more stable with smaller root-mean-square deviations and more accurate lattice atomic fluctuations compared with the crystallographic B-factors than under AMBER99SB force field.

Molecular Origin of the Self-Assembled Morphological Difference Caused by Varying the Order of Charged Residues in Short Peptides

Li Deng, Peng Zhou, Yurong Zhao, Yanting Wang, and Hai Xu [China University of Petroleum (East China)]

J. Phys. Chem. B., **118**, 12501–12510, 2014.

In order to understand how microscopic molecular interactions between short peptides determine their mesoscopic self-assembled morphology, we studied the microscopic assembled structures of the short peptides I4K2 and KI4K, which have the same amino acid composition but different sequences, by using all-atom replica exchange molecular dynamics simulation. We found that, at room temperature, the difference in amino acid sequence does not apparently alter their strong propensity of forming β -sheets but does strongly affect their assembled stable structures and their appearance probabilities.

Mechanistic insights into Pin1 peptidyl-prolyl cis-trans isomerization from umbrella sampling simulations

Giovanni Paolo Di Martino, Matteo Masetti [Alma Mater Studiorum—Università di Bologna], Andrea Cavalli and Maurizio Recanatini

Proteins: Stru. Fun. & Bioinf., **82**, 2943–2956, 2014.

The peptidyl-prolyl isomerase Pin1 plays a key role in the regulation of phospho(p)-Ser/Thr-Pro proteins, acting as a molecular timer of the cell cycle. After recognition of these motifs, Pin1 catalyzes the rapid cis-trans isomerization of proline amide bonds of substrates, contributing to maintain the equilibrium between the two conformations. Although a great interest has arisen on this enzyme, its catalytic mechanism has long been debated. Here, the cis-trans isomerization of a model peptide system was investigated by means of umbrella sampling simulations in the Pin1-bound and unbound states.

Molecular dynamic studies on the impact of mutations on the structure, stability, and N-terminal orientation of annexin A1: Implications for membrane aggregation

Bradley Simpkins, Matthew P. Donohue and Yumin Li [East Carolina University, Greenville]

Proteins: Stru. Fun. & Bioinf., **82**, 3327–3334, 2014.

Multiple MD simulations were performed for the full-length wild-type A1, the full length A1 mutations S27E and S27A, as well as the N-terminal peptide (AMVSEFLKQAWFIDNEEQEYIKTVKGS²⁷ KGGPGSAVSPYPTFN) of wild-type A1 and mutations S27E and S27A. The MD simulation trajectories of about 350 ns were generated and analyzed to examine the changes of core domain calcium binding affinity, core domain and N-terminal domain structures, and N-terminal domain orientation. Our results indicated that S27A and S27E mutations caused little changes on the calcium-binding affinity of the core domain of A1.

Monte Carlo

Tunable Coarse Graining for Monte Carlo Simulations of Proteins via Smoothed Energy Tables: Direct and Exchange Simulations

Justin Spiriti and Daniel M. Zuckerman [University of Pittsburgh]

J. Chem. Theor. and Comp., **10**, 5161–5177, 2014.

Many commonly used coarse-grained models for proteins are based on simplified interaction sites and consequently may suffer from significant limitations, such as the inability to properly model protein secondary structure without the addition of restraints. Recent work on a benzene fluid (Lettieri, S.; Zuckerman, D. M. *J. Comput. Chem.* 2012, 33, 268–275) suggested an alternative strategy of tabulating and smoothing fully atomistic orientation-dependent interactions among rigid molecules or fragments. Here we report our initial efforts to apply this approach to the polar and covalent interactions intrinsic to polypeptides.

QM and QM/MM

Adaptive-Partitioning QM/MM Dynamics Simulations: 3. Solvent Molecules Entering and Leaving Protein Binding Sites

Soroosh Pezeshki, Christal Davis, Andreas Heyden, and [University of Jinan]

J. Chem. Theor. and Comp., **10**, 4765–4776, 2014.

The adaptive-partitioning (AP) schemes for combined quantum-mechanical/molecular-mechanical (QM/MM) calculations allow on-the-fly reclassifications of atoms and molecules as QM or MM in dynamics simulations. The permuted-AP (PAP) scheme (*J. Phys. Chem. B* **2007**, 111, 2231) introduces a thin layer of buffer zone between the QM subsystem (also called active zone) and the MM subsystem (also known as the environmental zone) to provide a continuous and smooth transition and expresses the potential energy in a many-body expansion manner. The PAP scheme has been successfully applied to study small molecules solvated in bulk solvent.

POSSIM: Parameterizing Complete Second-Order Polarizable Force Field for Proteins

Xinbi Li, Sergei Y. Ponomarev, Daniel L. Sigalovsky, John P. Cvitkovic, and George A. Kaminski [Worcester Polytechnic Institute]

J. Chem. Theor. and Comp., **10**, 4896–4910, 2014.

Previously, we reported development of a fast polarizable force field and software named POSSIM (Polarizable Simulations with Second order Interaction Model). The second-order approximation permits the speed up of the polarizable component of the calculations by ca. an order of magnitude. We have now expanded the POSSIM framework to include a complete polarizable force field for proteins. Most of the parameter fitting was done to high-level quantum mechanical data. Conformational geometries and energies for dipeptides have been reproduced within average errors of ca. 0.5 kcal/mol for energies of the conformers (for the electrostatically neutral residues) and 9.7° for key dihedral angles.

 QM and QM/MM (Cont'd)

DNA Duplex Formation with a Coarse-Grained Model

Maciej Maciejczyk, Aleksandar Spasic, Adam Liwo, and Harold A. Scheraga [Baker Laboratory of Chemistry, Cornell University]

J. Chem. Theor. and Comp., **10**, 5020–5035, 2014.

A middle-resolution coarse-grained model of DNA is proposed. The DNA chain is built of spherical and planar rigid bodies connected by elastic virtual bonds. The bonded part of the potential energy function is fit to potentials of mean force of model systems. The rigid bodies are sets of neutral, charged, and dipolar beads. Electrostatic and van der Waals interactions are parametrized by our recently developed procedure [Maciejczyk, M.; Spasic, A.; Liwo, A.; Scheraga, H.A. *J. Comp. Chem.* **2010**, 31, 1644]. Interactions with the solvent and an ionic cloud are approximated by a multipole–multipole Debye–Hückel model.

MoD-QM/MM Structural Refinement Method: Characterization of Hydrogen Bonding in the Oxytrichina G-Quadruplex

Junming Ho, Michael B. Newcomer, Christina M. Ragain, Jose A. Gascon, Enrique R. Batista, J. Patrick Loria, and Victor S. Batista [Yale University]

J. Chem. Theor. and Comp., **10**, 5125–5135, 2014.

A generalization of the Moving-Domain Quantum Mechanics/Molecular Mechanics (MoD-QM/MM) hybrid method [Gascon, J. A.; Leung, S. S. F.; Batista, E. R.; Batista, V. S. *J. Chem. Theory Comput.* **2006**, 2, 175–186] is introduced to provide a self-consistent computational protocol for structural refinement of extended systems. The method partitions the system into molecular domains that are iteratively optimized as quantum mechanical (QM) layers embedded in their surrounding molecular environment to obtain an ab initio quality description of the geometry and the molecular electrostatic potential of the extended system composed of those constituent fragments.

Alternative Pathway for the Reaction Catalyzed by DNA Dealkylase AlkB from Ab Initio QM/MM Calculations

Dong Fang and G. Andrés Cisneros [Wayne State University, Detroit]

J. Chem. Theor. and Comp., **10**, 5136–5148, 2014.

AlkB is the title enzyme of a family of DNA dealkylases that catalyze the direct oxidative dealkylation of nucleobases. The conventional mechanism for the dealkylation of N1-methyl adenine (1-meA) catalyzed by AlkB after the formation of FeIV–oxo is comprised by a reorientation of the oxo moiety, hydrogen abstraction, OH rebound from the Fe atom to the methyl adduct, and the dissociation of the resulting methoxide to obtain the repaired adenine base and formaldehyde. An alternative pathway with hydroxide as a ligand bound to the iron atom is proposed and investigated by QM/MM simulations.

Structure and Dynamics of the Uranyl Tricarbonate Complex in Aqueous Solution: Insights from Quantum Mechanical Charge Field Molecular Dynamics

Andreas O. Tirlir and Thomas S. Hofer [University of Innsbruck]

J. Phys. Chem. B., **118**, 12938–12951, 2014.

This investigation presents the characterization of structural and dynamical properties of uranyl tricarbonate in aqueous solution employing an extended hybrid quantum mechanical/molecular mechanical (QM/MM) approach. It is shown that the inclusion of explicit solvent molecules in the quantum chemical treatment is essential to mimic the complex interaction occurring in an aqueous environment. Thus, in contrast to gas phase cluster calculations on a quantum chemical level proposing a 6-fold coordination of the three carbonates, the QMCF MD simulation proposes a 5-fold coordination.

QM and QM/MM (Cont'd)

Density functional theory calculations on entire proteins for free energies of binding: Application to a model polar binding site

Stephen J. Fox, Jacek Dziedzic, Thomas Fox, Christofer S. Tautermann and Chris-Kriton Skylaris [University of Southampton, Southampton]

Proteins: Stru. Fun. & Bioinf., **82**, 3335–3346, 2014.

In drug optimization calculations, the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method can be used to compute free energies of binding of ligands to proteins. The method involves the evaluation of the energy of configurations in an implicit solvent model. One source of errors is the force field used, which can potentially lead to large errors due to the restrictions in accuracy imposed by its empirical nature. To assess the effect of the force field on the calculation of binding energies, in this article we use large-scale density functional theory (DFT) calculations as an alternative method to evaluate the energies of the configurations in a “QM-PBSA” approach.

Ligand Docking

Detection of active transcription factor binding sites with the combination of DNase hypersensitivity and histone modifications

Eduardo G. Gusmao, Christoph Dieterich, Martin Zenke, and Ivan G. Costa [RWTH Aachen University Medical School]

Bioinformatics. **30**, 3143-3151, 2014.

The identification of active transcriptional regulatory elements is crucial to understand regulatory networks driving cellular processes such as cell development and the onset of diseases. It has recently been shown that chromatin structure information, such as DNase I hypersensitivity (DHS) or histone modifications, significantly improves cell-specific predictions of transcription factor binding sites. We propose here a method based on hidden Markov models to integrate DHS and histone modifications occupancy for the detection of open chromatin regions and active binding sites. We have created a framework that includes treatment of genomic signals, model training and genome-wide application.

Carbohydrate-binding protein identification by coupling structural similarity searching with binding affinity prediction

Huiying Zhao, Yuedong Yang, Mark von Itzstein and Yaoqi Zhou [Indiana University Purdue University]

J. Comp. Chem., **35**, 2177–2183, 2014.

Carbohydrate-binding proteins (CBPs) are potential biomarkers and drug targets. However, the interactions between carbohydrates and proteins are challenging to study experimentally and computationally because of their low binding affinity, high flexibility, and the lack of a linear sequence in carbohydrates as exists in RNA, DNA, and proteins. Here, we describe a structure-based function-prediction technique called SPOT-Struc that identifies carbohydrate-recognizing proteins and their binding amino acid residues by structural alignment program SPAlign and binding affinity scoring according to a knowledge-based statistical potential based on the distance-scaled finite-ideal gas reference state (DFIRE).

Ligand Docking (Cont'd)

Molecular Simulations with Solvent Competition Quantify Water Displaceability and Provide Accurate Interaction Maps of Protein Binding Sites

Daniel Alvarez-Garcia and Xavier Barril [Universitat de Barcelona]

J.Med.Chem., **57**, 8530–8539, 2014.

Binding sites present well-defined interaction patterns that putative ligands must meet. Knowing them is essential to guide structure-based drug discovery projects. However, complex aspects of molecular recognition—such as protein flexibility or the effect of aqueous solvation—hinder accurate predictions. This is particularly true for polar contacts, which are heavily influenced by the local environment and the behavior of discrete water molecules. Here we present and validate MDmix (Molecular Dynamics simulations with mixed solvents) as a method that provides much more accurate interaction maps than ordinary potentials (e.g., GRID).

Improving Docking Results via Reranking of Ensembles of Ligand Poses in Multiple X-ray Protein Conformations with MM-GBSA

P. A. Greenidge [Novartis Pharma AG], C. Kramer, J.-C. Mozziconacci, and W. Sherman

J.Chem. Infor. and Mod. **54**, 2697–2717, 2014.

There is a tendency in the literature to be critical of scoring functions when docking programs perform poorly. The assumption is that existing scoring functions need to be enhanced or new ones developed in order to improve the performance of docking programs for tasks such as pose prediction and virtual screening. In this work, we use the programs GOLD and Glide on a high-quality data set to explore whether failures in pose prediction and binding affinity estimation can be attributable more to sampling or scoring.

Ligand Efficiency-Based Support Vector Regression Models for Predicting Bioactivities of Ligands to Drug Target Proteins

Nobuyoshi Sugaya [PharmaDesign, Inc.,]

J.Chem. Infor. and Mod. **54**, 2751–2763, 2014.

The concept of ligand efficiency (LE) indices is widely accepted throughout the drug design community and is frequently used in a retrospective manner in the process of drug development. For example, LE indices are used to investigate LE optimization processes of already-approved drugs and to re-evaluate hit compounds obtained from structure-based virtual screening methods and/or high-throughput experimental assays. However, LE indices could also be applied in a prospective manner to explore drug candidates. Here, we describe the construction of machine learning-based regression models in which LE indices are adopted as an end point and show that LE-based regression models can outperform regression models based on pIC₅₀ values.

Perturbation of Fluid Dynamics Properties of Water Molecules during G Protein-Coupled Receptor–Ligand Recognition: The Human A_{2A} Adenosine Receptor as a Key Study

Davide Sabbadin, Antonella Ciancetta, and Stefano Moro [Università di Padova]

J.Chem. Infor. and Mod. **54**, 2846–2855, 2014.

Recent advances in structural biology revealed that water molecules play a crucial structural role in the protein architecture and ligand binding of G protein-coupled receptors. In this work, we present an alternative approach to monitor the time-dependent organization of water molecules during the final stage of the ligand–receptor recognition process by means of membrane molecular dynamics simulations. We inspect the variation of fluid dynamics properties of water molecules upon ligand binding with the aim to correlate the results with the binding affinities.

Ligand Docking (Cont'd)

Macromolecular Crowding Effects on Coupled Folding and Binding

Young C. Kim, Apratim Bhattacharya, and Jeetain Mittal
[Lehigh University, Bethlehem]

J. Phys. Chem. B., **118**, 12621–12629, 2014.

Replica exchange molecular dynamics simulations are performed on the protein complex pKID–KIX to understand the effects of macromolecular crowding on coupled folding and binding events. A structure-based protein model at the residue level is adopted for the two proteins to include intramolecular conformational flexibility, while crowding macromolecules are represented as spherical particles. The interactions between crowders and protein residues can be either purely repulsive or a combination of short-range repulsion and intermediate-range attraction.

3. JOURNAL REVIEWS

Journal of Computational Chemistry, 35 (29), November, 2014.

- 2087–2095 **Extension and validation of the GROMOS 53A6_{glyc} parameter set for glycoproteins**, Laercio Pol-Fachin, Hugo Verli and Roberto D. Lins [Federal University of Pernambuco]

See Methodology / Potentials and Parameters.

- 2096–2106 **Polarizable molecular mechanics studies of Cu(I)/Zn(II) superoxide dismutase: Bimetallic binding site and structured waters**, Nohad Gresh [Nucleo(s)tides and Immunology for Therapy (CBNIT)], Krystel El Hage, David Perahia, Jean-Philip Piquemal, Catherine Berthomieu and Dorothée Berthomieu

The existence of a network of structured waters in the vicinity of the bimetallic site of Cu/Zn-superoxide dismutase (SOD) has been inferred from high-resolution X-ray crystallography. Long-duration molecular dynamics (MD) simulations could enable to quantify the lifetimes and possible interchanges of these waters between themselves as well as with a ligand diffusing toward the bimetallic site.

- 2107–2113 **Electronic spectra and intersystem spin-orbit coupling in 1,2- and 1,3-squaraines**, Marta E. Alberto, Gloria Mazzone [Università della Calabria], Angelo D. Quartarolo, Flavio Fortes Ramos Sousa, Emilia Sicilia and Nino Russo

The main photophysical properties of a series of recently synthesized 1,2- and 1,3-squaraines, including absorption electronic spectra, singlet-triplet energy gaps, and spin-orbit matrix elements, have been investigated by means of density functional theory (DFT) and time-dependent DFT approaches.

- 2114–2121 **Using chiral molecules as an approach to address low-druggability recognition sites**, Xavier Lucas and Stefan Günther [University of Freiburg]

The content of chiral carbon atoms or structural complexity, which is known to correlate well with relevant physicochemical properties of small molecules, represents a promising descriptor that could fill the gap in existing drug discovery between ligand library filtering rules and the corresponding properties of the target's recognition site. Herein, we present an *in silico* study on the yet unclear underlying correlations between molecular complexity and other more sophisticated physicochemical and biological properties.

- 2122–2131 **The solvent effect on two competing reaction mechanisms involving hypervalent iodine reagents (λ^3 -iodanes): Facing the limit of the stationary quantum chemical approach**, Oliver Sala, Hans Peter Lüthi [Laboratorium für Physikalische Chemie] and Antonio Togni

Trifluoromethylation of acetonitrile with 3,3-dimethyl-1-(trifluoromethyl)-1 λ^3 ,2- benziiodoxol is assumed to occur via reductive elimination (RE) of the electrophilic CF₃-ligand and MeCN bound to the hypervalent iodine. Computations in gas phase showed that the reaction might also occur via an S_N2 mechanism.

- 2132–2139 **A new set of atomic radii for accurate estimation of solvation free energy by Poisson–Boltzmann solvent model**, Junya Yamagishi, Noriaki Okimoto [Quantitative Biology Center (QBiC)], Gentaro Morimoto and Makoto Taiji

See Methodology / Solvation Energy.

- 2140–2145 **Controlling the oxidative addition of aryl halides to Au(I)**, Israel Fernández [Radboud University Nijmegen], Lando P. Wolters and F. Matthias Bickelhaupt

By means of density functional theory calculations, we computationally analyze the physical factors governing the oxidative addition of aryl halides to gold(I) complexes.

- 2146–2161 **Geometrical and optical benchmarking of copper(II) guanidine–quinoline complexes: Insights from TD-DFT and many-body perturbation theory (part II)**, Alexander Hoffmann, Martin Rohrmüller, Anton Jesser, Ines dos Santos Vieira, Wolf Gero Schmidt and Sonja Herres-Pawlis [Ludwig-Maximilians-Universität München]

Ground- and excited-state properties of copper(II) charge-transfer systems have been investigated starting from density-functional calculations with particular emphasis on the role of (i) the exchange and correlation functional, (ii) the basis set, (iii) solvent effects, and (iv) the treatment of dispersive interactions.

Journal of Computational Chemistry, 35 (30), November, 2014.

- 2163–2176 **Efficiency of perturbation-selection and its orbital dependence in the SAC-CI calculations for valence excitations of medium-size molecules**, Ryoichi Fukuda and Masahiro Ehara [Research Center for Computational Science, Myodaiji]

The efficiency and accuracy of the perturbation-selection used in the symmetry-adapted cluster-configuration interaction (SAC-CI) calculations are investigated for several low-lying valence excited states of 21 medium-size molecules, including typical chromophores with heterocyclic macrocycles (free-base porphine, coumarin, indole, and BODIPY), nucleobases, amino acids (tyrosine and tryptophan), polycyclic aromatic hydrocarbons, and organometallics (ferrocene and $\text{Re}(\text{bpy})(\text{CO})_4^+$).

- 2177–2183 **Carbohydrate-binding protein identification by coupling structural similarity searching with binding affinity prediction**, Huiying Zhao, Yuedong Yang, Mark von Itzstein and Yaoqi Zhou [Indiana University Purdue University]

See Methodology / Ligand Docking.

- 2184–2194 **Distinguishing between keto–enol and acid–base forms of firefly oxyluciferin through calculation of excited-state equilibrium constants**, Olle Falklöf and Bo Durbeej [Linköping University]

Although recent years have seen much progress in the elucidation of the mechanisms underlying the bioluminescence of fireflies, there is to date no consensus on the precise contributions to the light emission from the different possible forms of the chemiexcited oxyluciferin (OxyLH_2) cofactor. Here, this problem is investigated by the calculation of excited-state equilibrium constants in aqueous solution for keto–enol and acid–base reactions connecting six neutral, monoanionic and dianionic forms of OxyLH_2 .

- 2195–2204 **A DFT study on proton transfers in hydrolysis reactions of phosphate dianion and sulfate monoanion**, Shinichi Yamabe [Kyoto University], Guixiang Zeng, Wei Guan and Shigeyoshi Sakaki

B3LYP calculations were carried out on hydrolysis reactions of monosubstituted(R) phosphate dianion and sulfate monoanion. In the reacting system, water clusters (H₂O)₂₂ and (H₂O)₃₅ are included to trace reaction paths.

- 2205–2214 **Exploiting space-group symmetry in fragment-based molecular crystal calculations**, Yonaton Heit and Gregory J. O. Beran [University of California, Riverside]

Recent developments in fragment-based methods make it increasingly feasible to use high-level ab initio electronic structure techniques to molecular crystals. Such studies remain computationally demanding, however. Here, we describe a straightforward algorithm for exploiting space-group symmetry in fragment-based methods which often provides computational speed-ups of several fold or more.

- 2215–2224 **Bayesian inference of conformational state populations from computational models and sparse experimental observables**, Vincent A. Voelz [Temple University, Philadelphia] and Guangfeng Zhou

We present a Bayesian inference approach to estimating conformational state populations from a combination of molecular modeling and sparse experimental data. Unlike alternative approaches, our method is designed for use with small molecules and emphasizes high-resolution structural models, using inferential structure determination with reference potentials, and Markov Chain Monte Carlo to sample the posterior distribution of conformational states.

- 2225–2230 **A spherical harmonic transform spectral analysis of a localized surface plasmon on a gold nano shell**, Dan Berco and Chin-Kun Hu [Complex System Group, Academia Sinica]

We perform a study of the localized surface plasmon (LSP) modes of a gold nano shell having a silica core by means of discrete dipole approximation (DDA) and spherical harmonics transform for selected wavelengths. We demonstrate an efficient solution for the near and intermediate field terms by the dyadic Green function approach and determine the optical extinction efficiency by the far field term.

Journal of Computational Chemistry, 35 (31), December, 2014.

- 2231–2238 **Melting of icosahedral nickel clusters under hydrostatic pressure**, Bing Fu, Li Chen, Feifei Wang, Yiqun Xie and Xiang Ye [Shanghai Normal University]

The thermal stabilities and melting behavior of icosahedral nickel clusters under hydrostatic pressure have been studied by constant-pressure molecular dynamics simulation. The potential energy and Lindemann index are calculated.

- 2239–2244 **Impact of Mn on the solution enthalpy of hydrogen in austenitic Fe-Mn alloys: A first-principles study**, Jörg von Appen, Richard Dronskowski, Aurab Chakrabarty, Tilmann Hickel [Max-Planck Institut für Eisenforschung GmbH], Robert Spatschek and Jörg Neugebauer

Hydrogen interstitials in austenitic Fe-Mn alloys were studied using density-functional theory to gain insights into the mechanisms of hydrogen embrittlement in high-strength Mn steels. The investigations reveal that H atoms at octahedral interstitial sites prefer a local environment containing Mn atoms rather than Fe atoms.

- 2245–2255 **GneimoSim: A modular internal coordinates molecular dynamics simulation package**, Adrien B. Larsen, Jeffrey R. Wagner, Saugat Kandel, Romelia Salomon-Ferrer, Nagarajan Vaidehi and Abhinandan Jain [California Institute of Technology]

See Applications / Bioinformatics.

- 2256–2262 **Efficient calculation of relative binding free energies by umbrella sampling perturbation**, Fabian Zeller and Martin Zacharias [Technische Universität München]

See Applications / Free Energy Calculations.

- 2263–2271 **van der Waals corrected density functional calculations of the adsorption of benzene on the Cu (111) surface**, Damien J. Carter [Curtin University] and Andrew L. Rohl

We investigate the performance of several van der Waals (vdW) functionals at calculating the interactions between benzene and the copper (111) surface, using the local orbital approach in the SIESTA code. We demonstrate the importance of using surface optimized basis sets to calculate properties of pure surfaces, including surface energies and the work function.

- 2272–2278 **Grid-based algorithm to search critical points, in the electron density, accelerated by graphics processing units**, Raymundo Hernández-Esparza, Sol-Milena Mejía-Chica, Andy D. Zapata-Escobar, Alfredo Guevara-García, Apolinar Martínez-Melchor, Julio-M. Hernández-Pérez, Rubicelia Vargas and Jorge Garza [Universidad Autónoma Metropolitana-Iztapalapa]

Using a grid-based method to search the critical points in electron density, we show how to accelerate such a method with graphics processing units (GPUs). When the GPU implementation is contrasted with that used on central processing units (CPUs), we found a large difference between the time elapsed by both implementations: the smallest time is observed when GPUs are used.

Journal of Computational Chemistry, 35 (32), December, 2014.

- 2279–2287 **Scents and sense: In silico perspectives on olfactory receptors**, Charleen G. Don and Sereina Riniker [Swiss Federal Institute of Technology]

See Applications / Bioinformatics.

- 2288–2296 **Structural evolution of small gold clusters doped by one and two boron atoms**, Rafael Grande-Aztatzi, Paulina R. Martínez-Alanis, José Luis Cabellos, Edison Osorio, Ana Martínez and Gabriel Merino [Centro de Investigación y de Estudios Avanzados Unidad Mérida]

The potential energy surfaces (PES) of a series of gold-boron clusters with formula Au_nB ($n = 1-8$) and Au_mB_2 ($m = 1-7$) have been explored using a modified stochastic search algorithm.

- 2297–2304 **Enhanced sampling simulations of DNA step parameters**, Aleksandra Karolak and Arjan van der Vaart [University of South Florida]

See Applications / Nucleic Acids.

- 2305–2318 **Lightweight object oriented structure analysis: Tools for building tools to analyze molecular dynamics simulations**, Tod D. Romo, Nicholas Leioatts and Alan Grossfield [University of Rochester Medical Center]

See Applications / Bioinformatics.

- 2319–2332 **Molecular dynamics simulation of configurational ensembles compatible with experimental FRET efficiency data through a restraint on instantaneous FRET efficiencies**, Maria M. Reif and Chris Oostenbrink [University of Natural Resources and Life Sciences]

See Applications / Protein Confirmation Analysis.

- 2333–2342 **Why it is sometimes difficult to determine the accurate position of a hydrogen atom by the semiexperimental method: Structure of molecules containing the OH or the CH₃ group**, Natalja Vogt, Jean Demaison [University of Ulm], Jürgen Vogt and Heinz Dieter Rudolph

The semiexperimental (SE) technique, whereby equilibrium rotational constants are derived from experimental ground-state rotational constants and corrections based on an ab initio cubic force field, has the reputation to be one of the most accurate methods to determine an equilibrium structure (r_e^{SE}).

Journal of Molecular Modeling, 20 (11), November, 2014.

- 2515 **Discovery of novel covalent proteasome inhibitors through a combination of pharmacophore screening, covalent docking, and molecular dynamics simulations**, Aibo Li, Haopeng Sun, Lei Du, Xiaoxin Wu, Jianqin Cao, Qidong You, Yuyan Li [China Pharmaceutical University]

See Applications / Medicinal Chemistry and Drug Design.

- 2513 **Protein modeling and molecular dynamics simulation of the two novel surfactant proteins SP-G and SP-H**, Felix Rausch [Friedrich Alexander University Erlangen-Nuremberg], Martin Schicht, Lars Bräuer, Friedrich Paulsen, Wolfgang Brandt

See Applications / Surfaces, Catalysts and Material Subjects.

- 2512 **Monte Carlo simulation of mixed nonionic Brij surfactants in water**, Ruzanna Yahya, Roghayeh Abedi Karjiban [Universiti Putra Malaysia], Mahiran Basri, Mohd Basyaruddin Abdul Rahman, Mauricio Girardi

See Applications / General and Model Systems.

- 2510 **Physical meaning of the QTAIM topological parameters in hydrogen bonding**, Darío J. R. Duarte [Universidad Nacional del Nordeste], Emilio L. Angelina, Néida M. Peruchena

This work examined the local topological parameters of charge density at the hydrogen bond (H-bond) critical points of a set of substituted formamide cyclic dimers and enolic tautomers. The analysis was performed not only on the total electron density of the hydrogen bonded complexes but also on the intermediate electron density differences derived from the Morokuma energy decomposition scheme.

- 2509 **DFT study of the effect of solvent on the H-atom transfer involved in the scavenging of the free radicals $\bullet\text{HO}_2$ and $\bullet\text{O}_2^-$ by caffeic acid phenethyl ester and some of its derivatives**, Olivier Holtomo, Mama Nsangou [University of Maroua], Jean Jules Fifen, Ousmanou Motapon

H-atom transfer from caffeic acid phenethyl ester (CAPE), MBC (3-methyl-2-butenyl caffeate), BC (benzoic caffeate), P3HC (phenethyl-3-hydroxycinnamate), and P4HC (phenethyl-4-hydroxycinnamate) to the selected free radicals $\bullet\text{HO}_2$ and $\bullet\text{O}_2^-$ was studied. Such a transfer can proceed in three different ways: concerted proton-coupled electron transfer (CPCET), electron transfer followed by proton transfer (ET-PT), and proton transfer followed by electron transfer (PT-ET).

- 2507 **Metal-doped graphene layers composed with boron nitride-graphene as an insulator: a nano-capacitor**, Majid Monajjemi [Islamic Azad University, Tehran]

A model of a nanoscale dielectric capacitor composed of a few dopants has been investigated in this study. This capacitor includes metallic graphene layers which are separated by an insulating medium containing a few h-BN layers.

- 2506 **A computational study on the photoelectric properties of various Bi_2O_3 polymorphs as visible-light driven photocatalysts**, Fang Wang [Southwest Petroleum University], Kun Cao, Qian Zhang, Xuedong Gong, Ying Zhou

This paper presents first-principle studies on the photoelectric properties of various Bi_2O_3 polymorphs. The intrinsic reason of different photocatalytic activities was revealed by electronic structures and optical features.

- 2505 **Molecular dynamics simulations of the mechanical properties of monoclinic hydroxyapatite**, Xiang Ou, Qiang Han [South Chian University of Technology]

Inorganic biomedical materials are of great interest in the biomedical field. One such material, hydroxyapatite (HAP), is the main inorganic substance in the hard tissue of bones and teeth in the human body. Here, we present the mechanical properties and new charges of the monoclinic form of HAP using the self-consistent charge equilibration (QEq) scheme proposed by Rappé and Goddard in 1991 (J Phys Chem 95:3358–3363), and a successful MD simulation of the uniaxially tensile and compressive properties of monoclinic HAP.

- 2504 **Three model shapes of Doxorubicin for liposome encapsulation**, Kanes Sumetpipat [Mahidol University], Duangkamon Baowan

See Applications / Medicinal Chemmistry and Drug Design.

- 2503 **Benchmarking coupled cluster methods on singlet excited states of nucleobases**, Dániel Kánnár, Péter G. Szalay [Eötvös University]

In this paper, coupled cluster methods CC2, CCSD, CCSDR(3) and EOM-CCSD(T) have been benchmarked against CC3 for the transition energies of nucleobases. Beside presenting vertical excitation energies for about 30 singlet transitions of four molecules, the results are analyzed statistically and problematic cases have been discussed in detail.

- 2502 **Understanding the effects of the number of pyrazines and their positions on charge-transport properties in silylethynylated N-heteropentacenes**, Shou-Feng Zhang, Xian-Kai Chen, Jian-Xun Fan, Jing-Fu Guo, Ai-Min Ren [Jilin University, Changchun], Yu-Wei Li

The charge-transport properties of a series of silylethynylated N-heteropentacenes (TIPS-PEN-xN; x = 2, 4) were systematically investigated using Marcus electron-transfer theory coupled with kinetic Monte Carlo simulations. Electronic structure calculations showed that introducing more pyrazine rings decreases the energy levels of the lowest unoccupied molecular orbitals (LUMOs) and should aid electron transfer.

- 2501 **Emulating structural stability of *Pseudomonas mendocina* lipase: in silico mutagenesis and molecular dynamics studies**, Parameswaran Saravanan, Vikash Kumar Dubey, Sanjukta Patra [Indian Institute of Technology Guwahati]

See Applications / Medicinal Chemistry and Drug Design.

- 2500 **Understanding the recognition mechanisms of Z α domain of human editing enzyme ADAR1 (hZ α _{ADAR1}) and various Z-DNAs from molecular dynamics simulation**, Qianqian Wang, Lanlan Li, Xiaoting Wang, Huanxiang Liu [Lanzhou University], Xiaojun Yao

See Applications / Nucleic Acids.

- 2499 **Contribution of phenylalanine side chain intercalation to the TATA-box binding protein–DNA interaction: molecular dynamics and dispersion-corrected density functional theory studies**, Manas Mondal, Sanchita Mukherjee, Dhananjay Bhattacharyya [Saha Institute of Nuclear Physics]

See Applications / Protein-Nucleic acids.

- 2497 **Characteristics of protein residue-residue contacts and their application in contact prediction**, Pawel P. Wozniak, Malgorzata Kotulska [Wroclaw University of Technology]

See Methodology / Potentials and Parameters.

- 2496 **A molecular simulation study of the protection of insulin bioactive structure by trehalose**, Daixi Li [University of Shanghai for Science and Technology], Li Liu, Huaxing Yu, Zhen Zhai, Yan Zhang, Baisong Guo, Chunsheng Yang, Baolin Liu

See Applications / Protein Dynamics.

- 2495 **Interaction between phosphomolybdate anion and imidazolium cation in polyoxometalates-based ionic liquids: a quantum mechanics study**, Yi Zheng, Jun Liu, Xiaoning Yang [Nanjing University of Technology], Jun Wang

In this study, interaction between the phosphomolybdic anions ($[\text{PMoO}]^{3-}$) and 1-butyl-3-methyl imidazolium cations ($[\text{Bmim}]^+$) has been systematically studied by the density functional theory at the PBE-D3/TZP level. The stable geometries of the ion pairs with no imaginary frequencies were obtained and characterized.

- 2494 **Ab initio Molecular orbital and density functional studies on the ring-opening reaction of oxetene**, S. Jayaprakash [Islamiah College, Vaniyambadi], Jebakumar Jeevanandam, K. Subramani

Electrocyclic ring opening (ERO) reaction of 2H-Oxete (oxetene) has been carried out computationally in the gas phase and ring opening barrier has been computed. When comparing the ERO reaction of oxetene with the parent hydrocarbon (cyclobutene), the ring opening of cyclobutene is found to exhibit pericyclic behavior while oxetene shows mild pseudopericyclic nature.

- 2493 **Competition between π -hole interaction and hydrogen bond in the complexes of F_2XO ($\text{X} = \text{C}$ and Si) and HCN** , Xin Guo, Lishui Cao, Qingzhong Li [Yantai University], Wenzuo Li, Jianbo Cheng

Complexes $\text{F}_2\text{XO} \cdots \text{HCN}$ ($\text{X} = \text{C}$ and Si) have been studied by quantum chemical calculations at the MP2/aug-cc-pVTZ level to investigate the competition between π -hole interaction and hydrogen bond. F_2XO has a dual role of a Lewis acid and base with the π -hole on the X atom and the O atom to participate in the π -hole interaction and hydrogen bond with HCN , respectively.

- 2492 **Introducing “UCA-FUKUI” software: reactivity-index calculations**, Jesús Sánchez-Márquez [Campus Universitario Río San Pedro], David Zorrilla, Antonio Sánchez-Coronilla, Desireé M. de los Santos, Javier Navas, Concha Fernández-Lorenzo, Rodrigo Alcántara, Joaquín Martín-Calleja

A new software (UCA-FUKUI) has been developed to facilitate the theoretical study of chemical reactivity. This program can calculate global parameters like hardness, softness, philicities, and Fukui condensed functions, and also local parameters from the condensed functions.

- 2491 **Understanding the effects on constitutive activation and drug binding of a D130N mutation in the $\beta 2$ adrenergic receptor via molecular dynamics simulation**, Yanyan Zhu, Yuan Yuan, Xiuchan Xiao, Liyun Zhang, Yanzhi Guo, Xuemei Pu [Sichuan University]

See Applications / Medicinal Chemmistry and Drug Design.

- 2490 **Chemisorption-induced two- to three-dimensions structural transformations in gold pentamer $(\text{CO})_n\text{Au}_5^-$ ($n = 0-5$)**, Ming-Min Zhong [Southwest University, Chongqing], Xiao-Yu Kuang, Zhen-Hua Wang, Hong-kuan Yuan, Hong Chen

Understanding the geometry structures of gold clusters, especially with adsorbates, is essential for designing highly active gold nanocatalysts. Here, CO chemisorption onto the Au_5^- cluster is investigated using the density functional calculations.

- 2489 **Computational study on the effects of substituent and heteroatom on physical properties and solar cell performance in donor-acceptor conjugated polymers based on benzodithiophene**, Lvyong Zhang, Wei Shen, Rongxing He, Xiaorui Liu, Zhiyong Fu, Ming Li [Southwest University, Chongqing]

Computationally driven material design has attracted increasing interest to accelerate the search for optimal conjugated donor materials in bulk heterojunction organic solar cells. A series of novel copolymers containing benzo[1,2-b:4,5-b']dithiophene (BDT) and thieno[3,4-c]pyrrole-4,6-dione (TPD) derivatives were simulated by density functional theory (DFT) and time-dependent density functional theory (TD-DFT).

- 2488 **Theoretical study on the properties and stabilities of complexes formed between SO₄ (C2v) and isostructure species of CO₂, CS₂, and SCO**, Abdolvahab Seif, Shokofeh Massahi [Ilam University]

In this work ab initio calculations at MP2 level in conjugation with aug-cc-pVXZ (X=D and T) basis set were performed in order to examine complexes formed between SO₄ and each of linear molecules of CO₂, CS₂, and SCO. The results have been discussed on real minima located on singlet potential energy surface (PES).

- 2486 **Deformation density components analysis of fullerene-based anti-HIV drugs**, Sara Fakhraee [Payame Noor University], Maryam Sour

See Applications / Medicinal Chemmistry and Drug Design.

- 2485 **Conformation and dynamics of 8-Arg-vasopressin in solution**, Elke Haensele, Lee Banting, David C. Whitley, Timothy Clark [University of Portsmouth]

See Applications / Protein Confirmation Analysis.

- 2484 **Density functional theory (DFT) study of the gas-phase decomposition of the Cd[(ⁱPr)₂PSSe]₂ single-source precursor for the CVD of binary and ternary cadmium chalcogenides**, Francis Opoku, Noah Kyame Asare-Donkor, Anthony A. Adimado [Kwame Nkrumah University of Science and Technology]

The chemistry of group II–VI semiconductors has spurred considerable interest in decomposition reaction mechanisms and has been exploited for various technological applications. In this work, computational chemistry was employed to investigate the possible gas-phase decomposition pathways of the mixed Cd[(ⁱPr)₂PSSe]₂ single-source precursor for the chemical vapour deposition of cadmium chalcogenides as thin films.

- 2483 **Searching for a new family of insensitive high explosives by introducing N hybridization and N-oxides into a cage cubane**, Qiong Wu, Weihua Zhu [Nanjing University of Science and Technology], Heming Xiao

A new family of energetic azacubane N-oxides were designed by introducing N-oxides into azacubanes and investigated by using density functional theory. Introducing the N-oxides into the azacubanes could improve their detonation performance significantly due to the increase of the OB and ρ but would also increase the sensitivity to some extent.

- 2482 **An insight into the structures, stabilities, and bond character of B_nPt (n=1~6) clusters**, Guangli Yang, Wenwen Cui, Xiaolei Zhu [Nanjing University of Technology], Ruiying Yue

We perform a systematical investigation on the geometry, thermodynamic/kinetic stability, and bonding nature of low-lying isomers of B_nPt (n=1-6) at the CCSD(T)/[6-311+G(d)/LanL2DZ]/B3LYP/[6-311+G(d)/LanL2DZ] level.

- 2481 **Size dependent structural, electronic, and magnetic properties of Sc_N (N=2-14) clusters investigated by density functional theory**, Snehasis Bhunia, Nidhi Vyas, Chandan Sahu, Animesh K. Ojha [Motilal Nehru National Institute of Technology]

Structural, electronic, and magnetic properties of Sc_N ($N=2-14$) clusters have been investigated using density functional theory (DFT) calculations. Different spin states isomer for each cluster size has been optimized with symmetry relaxation.

- 2480 **Theoretical investigation of hydrogen bonding interaction in $\text{H}_3\text{O}^+(\text{H}_2\text{O})_9$ complex**, Gul Afroz Meraj, Ajay Chaudhari [The Institute of Science, FORT, Mumbai]

Hydrogen bonding interaction of hydronium ion with water molecules in its first and second solvation shell is studied using density functional theory with B3LYP functional and aug-cc-pvtz basis set. The nature of interaction and contribution from various interaction energies to the binding energy of a complex is studied using many-body analysis approach.

- 2479 **Design and theoretical study of 15 novel high energy density compounds**, Wei-peng Lai [Xi'an modern chemistry research institute], Peng Lian, Ying-zhe Liu, Tao Yu, Wei-liang Zhu, Zhong-xue Ge, Jian Lv

In order to seek the potential high energy density compounds (HEDCs) with excellent performance and satisfactory safety, some combination rules are presented and 15 HEDCs are designed and sifted, and followed by the properties predicting.

- 2478 **A consistent force field parameter set for zwitterionic amino acid residues**, Anselm H. C. Horn [Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU)]

See Methodology / Potentials and Parameters.

- 2477 **Hydrogen-bonded complexes between dimethyl sulfoxide and monoprotic acids: molecular properties and IR spectroscopy**, Márcia K. D. L. Belarmino, Vanessa F. Cruz, Nathália B. D. Lima [Universidade Federal de Pernambuco (UFPE)]

MP2/6-31++G(d,p) and DFT B3LYP/6-31++G(d,p) calculations were performed of the structure, binding energies, and vibrational modes of complexes between dimethyl sulfoxide (DMSO) as a proton acceptor and monoprotic linear acids HX ($X = \text{F}, \text{Cl}, \text{CN}$) as well as monoprotic carboxylic acids HOOCR ($R = -\text{H}, -\text{CH}_3, -\text{C}_6\text{H}_5$) in 1:1 and 1:2 stoichiometric ratios.

- 2473 **The role of NH_3 and hydrocarbon mixtures in GaN pseudo-halide CVD: a quantum chemical study**, Oleg B. Gadzhiev [Russian Academy of Sciences], Peter G. Sennikov, Alexander I. Petrov, Krzysztof Kachel, Sebastian Golka, Daniela Gogova, Dietmar Siche

The prospects of a control for a novel gallium nitride pseudo-halide vapor phase epitaxy (PHVPE) with HCN were thoroughly analyzed for hydrocarbons- NH_3 -Ga gas phase on the basis of quantum chemical investigation with DFT (B3LYP, B3LYP with D3 empirical correction on dispersion interaction) and ab-initio (CASSCF, coupled clusters, and multireference configuration interaction including MRCI+Q) methods.

- 2472 **Conformational analysis of a polyconjugated protein-binding ligand by joint quantum chemistry and polarizable molecular mechanics. Addressing the issues of anisotropy, conjugation, polarization, and multipole transferability**, Elodie Goldwaser, Benoit de Courcy, Luc Demange, Christiane Garbay, Françoise Raynaud, Reda Hadj-Slimane, Jean-Philip Piquemal, Nohad Gresh [Université ParisDescartes]

See Applications / Protein Conformational Analysis.

- 2464 **Computational study of antimalarial pyrazole alkaloids from *Newbouldia laevis***, Liliana Mammino [University of Venda], Mireille K. Bilonda

Six pyrazole alkaloids of natural origin (isolated from *Newbouldia laevis* in DR Congo) that exhibit antimalarial activity—namely withasomnine, newbouldine, and their para-hydroxy and -methoxy derivatives—were investigated theoretically. The nitro derivatives of withasomnine and para-hydroxywithasomnine, which show enhanced antimalarial activity, were also studied in this manner.

- 2462 **The structures and stability of silylenoids RBrSiLi_2 ($\text{R}=\text{CH}_3$, $\text{C}(\text{SiH}_3)_3$)**, Yuhua Qi [University of Jinan], Chongjuan Xu, Bing Geng, Maoxia He

The structures and stabilities of RBrSiLi_2 ($\text{R}=\text{CH}_3$, $\text{C}(\text{SiH}_3)_3$) have been studied using ab initio and DFT methods. $\text{CH}_3\text{BrSiLi}_2$ and $\text{C}(\text{SiH}_3)_3\text{BrSiLi}_2$ have three possible structures, the p-complex, the plain, and the folded structures.

4. ADDRESSES OF PRINCIPAL AUTHORS

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